TITLE

SPIRO-CYCLIC β-AMINO ACID DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEINASES AND TNF-α CONVERTING ENZYME (TACE)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Divisional of U.S. Ser. No. 10/096,804, filed March 12, 2002, now allowed, which in turn claims the priority benefit of U.S. Provisional Application No. 60/275,898, filed March 15, 2001, all of which are expressly incorporated fully herein by reference.

FIELD OF THE INVENTION

This invention relates generally to novel spiro-cyclic β-amino acid derivatives as matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), and/or aggrecanase inhibitors, pharmaceutical compositions containing the same, and methods of using the same.

BACKGROUND OF THE INVENTION

There is now a body of evidence that metalloproteases (MP) are important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins

and TIMPs (tissue inhibitors of metalloprotease), which form inactive complexes with the MP's.

Osteo- and Rheumatoid Arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. *J. Bone Joint Surg.* **1970**, *52A*, 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteases. The available evidence supports that it is the metalloproteases that are responsible for the degradation of the extracellular matrix of articular cartilage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. *Arthritis Rheum.* **1978**, *21*, 761-766, Woessner et al. *Arthritis Rheum.* **1983**, *26*, 63-68 and Woessner et al. *Arthritis Rheum.* **1984**, *27*, 305-312). In addition, aggrecanase has been identified as providing the specific cleavage product of proteoglycan found in RA and OA patients (Lohmander L.S. et al. *Arthritis Rheum.* **1993**, *36*, 1214-22).

Therefore, metalloproteases (MP) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors, and many compounds have been suggested for this purpose (see Wahl et al. *Ann. Rep. Med. Chem.* **1990**, *25*, 175-184, AP, San Diego).

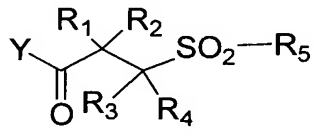
Tumor necrosis factor-α (TNF-α) is a cell-associated cytokine that is processed from a 26kd precursor form to a 17kd active form. TNF-α has been shown to be a primary mediator in humans and in animals, of inflammation, fever, and acute phase responses, similar to those observed during acute infection and shock. Excess TNF-α has been shown to be lethal. There is now considerable evidence that blocking the effects of TNF-α with specific antibodies can be beneficial in a variety of circumstances including autoimmune diseases such as rheumatoid arthritis (Feldman et al. *Lancet* **1994**, *344*, 1105), non-insulin dependent diabetes melitus (Lohmander, L.S. et al. *Arthritis Rheum.* **1993**, *36*, 1214-22) and Crohn's disease (MacDonald et al. *Clin. Exp. Immunol.* **1990**, *81*, 301).

Compounds which inhibit the production of TNF-α are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently, TNF-α converting enzyme (TACE), the enzyme responsible for TNF-α release from cells, were purified and sequenced (Black et al. *Nature* **1997**, *385*, 729; Moss et al. *Nature* **1997**, *385*, 733). This invention describes molecules that inhibit this enzyme and hence the secretion of active TNF-α from cells. These novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock, haemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, OA, RA, multiple sclerosis,

radiation damage, hyperoxic alveolar injury, periodontal disease, HIV and non-insulin dependent diabetes melitus.

Since excessive TNF-α production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF-α production may also have a particular advantage in diseases where both mechanisms are involved.

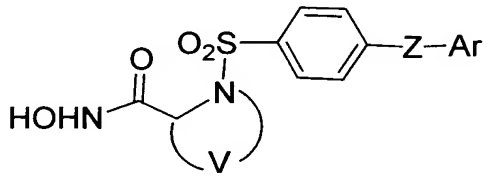
EP 0,780,286 describes MMP inhibitors of formula A:



A

wherein Y can be NHOH, R^1 and R^2 can combine to form a cycloalkyl or heterocyclo alkyl group, R^3 and R^4 can be a variety of groups including H, and R^5 can be substituted aryl.

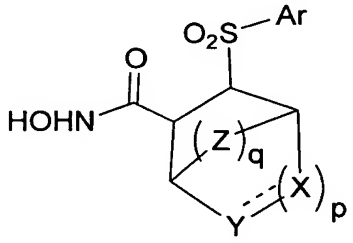
WO 97/20824 depicts MMP inhibitors of formula B:



B

wherein ring V contains six atoms, Z is O or S, and Ar is an aryl or heteroaryl group. Ar is preferably a monocyclic aryl group with an optional para substituent or an unsubstituted monocyclic heteroaryl group.

EP 0,818,442 illustrates MMP inhibitors of formula C:



C

wherein Ar is optionally substituted phenyl or naphthyl, Z can be absent and X and Y can be a variety of substituents. Compounds of this sort are not considered to be part of the present invention.

The compounds of the present invention act as inhibitors of MPs, in particular TACE, MMPs, and/or aggrecanase. These novel molecules are provided as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of aggrecanase, TACE, and other metalloproteases by molecules of the present invention indicates they are anti-inflammatory and should prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of OA and RA.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel spiro-cyclic hydroxamic acids useful as MMP, TACE, and/or aggrecanase inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating inflammatory disorders, comprising: administering to a host, in need of such treatment, a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method of treating a condition or disease

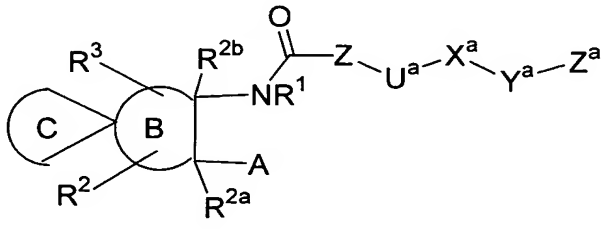
mediated by MMPs, TACE, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method comprising: administering a compound of the present invention or a pharmaceutically acceptable salt or prodrug form thereof in an amount effective to treat a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

It is another object of the present invention to provide novel compounds of the present invention for use in therapy.

It is another object of the present invention to provide the use of novel compounds of the present invention for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

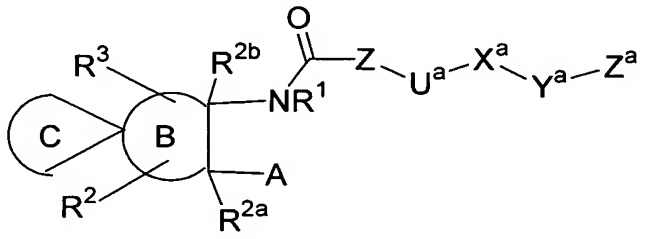


I

or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, C, R^1, R^2, R^{2a}, R^{2b}, R^3, Z, U^a, X^a, Y^a, and Z^a are defined below, are effective metalloprotease inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides a novel compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from $-COR^5$, $-CO_2H$, CH_2CO_2H, $-CO_2R^6$, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -N(OH)CHO, -SH, $-CH_2SH$, $-S(O)(=NH)R^a$, $-SN_2H_2R^a$, $-PO(OH)_2$, and $-PO(OH)NHR^a$;

ring B is a 3-13 membered non-aromatic carbocycle or heterocycle comprising: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 0-2 ring heteroatoms selected from O, N, NR^2, and $S(O)_p$, provided that ring B contains other than a S-S, O-O, or S-O bond;

ring C forms a spiro ring on Ring B and is a 3-13 membered carbocycle or heterocycle comprising: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 0-5 ring heteroatoms selected from O, N, NR^2, and $S(O)_p$ and substituted with 0-6 R^e, provided that ring C contains other than a S-S, O-O, or S-O bond;

Z is absent or selected from a C_{3-13} carbocycle substituted with 0-5 R^b and a 5-14 membered

heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-5 R^b;

U^a is absent or is selected from: O, NR^{a1}, C(O), C(O)O, OC(O), $C(O)NR^{a1}$, $NR^{a1}C(O)$, OC(O)O, $OC(O)NR^{a1}$, $NR^{a1}C(O)O$, $NR^{a1}C(O)NR^{a1}$, $S(O)_p$, $S(O)_pNR^{a1}$, $NR^{a1}S(O)_p$, and $NR^{a1}SO_2NR^{a1}$;

X^a is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Y^a is absent or selected from O, NR^{a1}, $S(O)_p$, and C(O);

Z^a is selected from H, a C_{3-13} carbocycle substituted with 0-5 R^c and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-5 R^c;

provided that Z, U^a, Y^a, and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$-O, O-$S(O)_p$ or $S(O)_p$-$S(O)_p$ group;

R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;

R^2 is selected from Q, Cl, F, (C_{1-10} alkylene substituted with 0-3 R^{b1})-Q, (C_{2-10} alkenylene substituted with 0-3 R^{b1})-Q, (C_{2-10} alkynylene substituted with 0-3 R^{b1})-Q, $(CR^aR^{a1})_{r1}O(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}NR^a(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}C(O)(CR^aR^{a1})_r$-Q,

$(CR^aR^{a1})_{r1}C(O)O(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}C(O)O$-C_{2-5} alkenylene,
$(CR^aR^{a1})_{r1}C(O)O$-C_{2-5} alkynylene,
$(CR^aR^{a1})_{r1}OC(O)(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}C(O)NR^aR^{a1}$,
$(CR^aR^{a1})_{r1}C(O)NR^a(CR^aR^{a1})_r$-Q,
$(CR^aR^{a1})_{r1}NR^aC(O)(CR^aR^{a1})_r$-Q,
$(CR^aR^{a1})_{r1}OC(O)O(CR^aR^{a1})_r$-Q,
$(CR^aR^{a1})_{r1}OC(O)NR^a(CR^aR^{a1})_r$-Q,
$(CR^aR^{a1})_{r1}NR^aC(O)O(CR^aR^{a1})_r$-Q,
$(CR^aR^{a1})_{r1}NR^aC(O)NR^a(CR^aR^{a1})_r$-Q,
$(CR^aR^{a1})_{r1}S(O)_p(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}SO_2NR^a(CR^aR^{a1})_r$-Q,
$(CR^aR^{a1})_{r1}NR^aSO_2(CR^aR^{a1})_r$-Q, and
$(CR^aR^{a1})_{r1}NR^aSO_2NR^a(CR^aR^{a1})_r$-Q;

R^{2a} is selected from H, C_{1-6} alkyl, OR^a, NR^aR^{a1}, and $S(O)_pR^a$;

R^{2b} is H or C_{1-6} alkyl;

Q is selected from H, a C_{3-13} carbocycle substituted with 0-5 R^d and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-5 R^d;

R^3 is selected from Q^1, Cl, F, C_{1-6} alkylene-Q^1, C_{2-6} alkenylene-Q^1, C_{2-6} alkynylene-Q^1,
$(CR^aR^{a1})_{r1}O(CR^aR^{a1})_r$-$Q^1$, $(CR^aR^{a1})_{r1}NR^a(CR^aR^{a1})_r$-$Q^1$,
$(CR^aR^{a1})_{r1}NR^aC(O)(CR^aR^{a1})_r$-$Q^1$,
$(CR^aR^{a1})_{r1}C(O)NR^a(CR^aR^{a1})_r$-$Q^1$,
$(CR^aR^{a1})_{r1}C(O)(CR^aR^{a1})_r$-$Q^1$, $(CR^aR^{a1})_{r1}C(O)O(CR^aR^{a1})_r$-$Q^1$,

$(CR^aR^{a1}{}_2)_{r1}S(O)_p(CR^aR^{a1})_r$-$Q^1$, and
$(CR^aR^{a1})_{r1}SO_2NR^a(CR^aR^{a1})_r$-$Q^1$;

Q^1 is selected from H, phenyl substituted with 0-3 R^d, naphthyl substituted with 0-3 R^d and a 5-10 membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-3 R^d;

R^a, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

R^{a1}, at each occurrence, is independently selected from H and C_{1-4} alkyl;

alternatively, R^a and R^{a1} when attached to a nitrogen are taken together with the nitrogen to which they are attached to form a 5 or 6 membered ring comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{a2}, at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;

R^b, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, and CF_2CF_3;

R^{b1}, at each occurrence, is independently selected from OR^a, Cl, F, Br, I, =O, -CN, NO_2, and NR^aR^{a1};

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, CH_2F, CHF_2, CF_2CH_3, $C(CH_3)_2F$, OCF_3, C_{3-10} carbocycle substituted with 0-3 R^{c1} and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-3 R^{c1};

alternatively, when two R^c groups are attached to the same carbon atom, they form a spiro ring D that is a 3-11 membered carbocycle substituted with 0-2 R^{c1} or a 3-13 membered heterocycle comprising: carbon atoms and from 1-4 ring heteroatoms selected from O, N, and $S(O)_p$ and substituted with 0-2 R^{c1}, provided that ring D contains other than a S-S, O-O, or S-O bond;

alternatively, when two R^c groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered saturated, partially saturated or unsaturated ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$; this ring is substituted with 0-2 R^{c1};

R^{c1}, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1},

$C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, CH_2F, and CHF_2;

R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, C_{3-10} carbocycle and a 5-14 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^e, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, C_{3-10} carbocycle substituted with 0-2 R^{c1}, $(CR^aR^{a1})_{r1}$-C_{3-10} carbocycle substituted with 0-2 R^{c1}, a 5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1}, and $(CR^aR^{a1})_{r1}$-5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1};

R^5, at each occurrence, is selected from C_{1-10} alkyl substituted with 0-2 R^b, and C_{1-8} alkyl substituted with 0-2 R^f;

R^f, at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b;

R^6, at each occurrence, is selected from phenyl, naphthyl, C_{1-10} alkyl-phenyl-C_{1-6} alkyl-, C_{3-11} cycloalkyl, C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxycarbonyloxy-C_{1-3} alkyl-, C_{2-10} alkoxycarbonyl, C_{3-6} cycloalkylcarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyl, phenoxycarbonyl, phenyloxycarbonyloxy-C_{1-3} alkyl-, phenylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxy-C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, [5-(C_1-C_5 alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl, [5-(R^a)-1,3-dioxa-cyclopenten-2-one-yl]methyl, (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, -C_{1-10} alkyl-NR^7R^{7a}, $-CH(R^8)OC(=O)R^9$, and $-CH(R^8)OC(=O)OR^9$;

R^7 is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^{7a} is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^8 is selected from H and C_{1-4} linear alkyl;

R^9 is selected from H, C_{1-8} alkyl substituted with 1-2 R^g, C_{3-8} cycloalkyl substituted with 1-2 R^g, and phenyl substituted with 0-2 R^b;

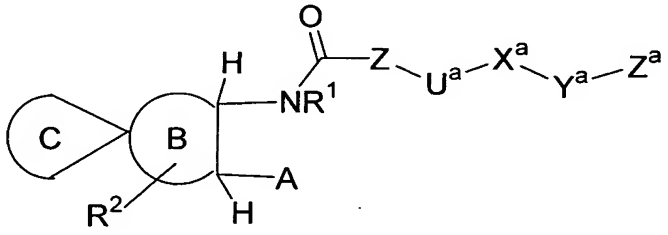
R^g, at each occurrence, is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-5} alkoxy, and phenyl substituted with 0-2 R^b;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,

r1, at each occurrence, is selected from 0, 1, 2, 3, and 4.

[2] In a preferred embodiment, the present invention provides a novel compound of formula II:



II

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from $-CO_2H$, CH_2CO_2H, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -N(OH)CHO, -SH, and $-CH_2SH$;

ring B is a 4-7 membered non-aromatic carbocyclic or heterocyclic ring comprising: carbon atoms, 0-1 carbonyl groups, 0-1 double bonds, and from 0-2 ring

heteroatoms selected from O, N, and NR^2, provided that ring B contains other than a O-O bond;

ring C forms a spiro ring on Ring B and is a 4-10 membered carbocycle substituted with 0-3 R^e or a 4-10 membered heterocycle comprising: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 0-4 ring heteroatoms selected from O, N, NR^2, and $S(O)_p$ and substituted with 0-3 R^e, provided that ring C contains other than a S-S, O-O, or S-O bond;

Z is absent or selected from a C_{3-11} carbocycle substituted with 0-4 R^b and a 5-11 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-3 R^b;

U^a is absent or is selected from: O, NR^{a1}, C(O), C(O)O, $C(O)NR^{a1}$, $NR^{a1}C(O)$, $S(O)_p$, and $S(O)_pNR^{a1}$;

X^a is absent or selected from C_{1-4} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene;

Y^a is absent or selected from O and NR^{a1};

Z^a is selected from H, a C_{3-10} carbocycle substituted with 0-5 R^c and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-5 R^c;

provided that Z, U^a, Y^a, and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$-O, O-$S(O)_p$ or $S(O)_p$-$S(O)_p$ group;

R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;

R^2 is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, C_{2-6} alkynylene-Q, $(CR^aR^{a1})_{r1}O(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}NR^a(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}C(O)(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}C(O)O(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_rC(O)NR^aR^{a1}$, $(CR^aR^{a1})_{r1}C(O)NR^a(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}S(O)_p(CR^aR^{a1})_r$-Q, and $(CR^aR^{a1})_{r1}SO_2NR^a(CR^aR^{a1})_r$-Q;

Q is selected from H, a C_{3-6} carbocycle substituted with 0-5 R^d, and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-5 R^d;

R^a, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

R^{a1}, at each occurrence, is independently selected from H and C_{1-4} alkyl;

alternatively, R^a and R^{a1} when attached to a nitrogen are taken together with the nitrogen to which they are attached to form a 5 or 6 membered ring comprising carbon atoms and from 0-1 additional heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{a2}, at each occurrence, is independently selected from C_{1-4} alkyl, phenyl and benzyl;

R^b, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, -CN, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, and CF_3;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, -CN, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, CF_3, CH_2F, CHF_2, CF_2CH_3, $C(CH_3)_2F$, OCF_3, C_{3-6} carbocycle substituted with 0-2 R^{c1} and a 5-6 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1};

alternatively, when two R^c groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-6 membered saturated, partially saturated or unsaturated ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^{c1}, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, CH_2F, and CHF_2;

R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, -CN, NR^aR^{a1}, $C(O)R^a$,

$C(O)OR^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, CF_3, C_{3-6} carbocycle and a 5-6 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^e, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, C_{3-10} carbocycle substituted with 0-2 R^{c1}, $(CR^aR^{a1})_{r1}$-C_{3-10} carbocycle substituted with 0-2 R^{c1}, a 5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1}, and $(CR^aR^{a1})_{r1}$-5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1};

R^5, at each occurrence, is selected from C_{1-6} alkyl substituted with 0-2 R^b, and C_{1-4} alkyl substituted with 0-2 R^f;

R^f, at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b;

R^6, at each occurrence, is selected from phenyl, naphthyl, C_{1-10} alkyl-phenyl-C_{1-6} alkyl-, C_{3-11} cycloalkyl, C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxycarbonyloxy-C_{1-3} alkyl-, C_{2-10} alkoxycarbonyl,

C_{3-6} cycloalkylcarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyl, phenoxycarbonyl, phenyloxycarbonyloxy-C_{1-3} alkyl-, phenylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxy-C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, [5-(C_1-C_5 alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl, [5-(R^a)-1,3-dioxa-cyclopenten-2-one-yl]methyl, (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, -C_{1-10} alkyl-NR^7R^{7a}, $-CH(R^8)OC(=O)R^9$, and $-CH(R^8)OC(=O)OR^9$;

R^7 is selected from H and C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^{7a} is selected from H and C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^8 is selected from H and C_{1-4} linear alkyl;

R^9 is selected from H, C_{1-6} alkyl substituted with 1-2 R^g, C_{3-6} cycloalkyl substituted with 1-2 R^g, and phenyl substituted with 0-2 R^b;

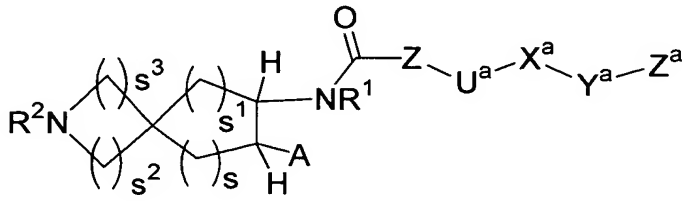
R^g, at each occurrence, is selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-5} alkoxy, and phenyl substituted with 0-2 R^b;

p, at each occurrence, is selected from 0, 1, and 2;

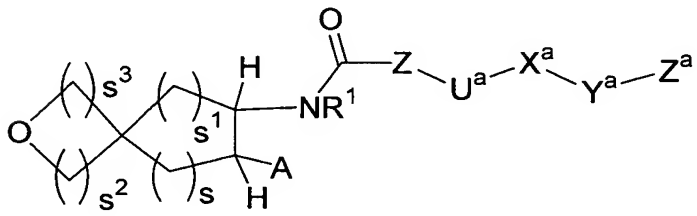
r, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,

r1, at each occurrence, is selected from 0, 1, 2, 3, and 4.

[3] In another preferred embodiment, the present invention provides a novel compound of formula IIIa or IIIb:



IIIa



IIIb

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from $-CO_2H$, CH_2CO_2H, $-CONHOH$, $-CONHOR^5$, $-N(OH)CHO$, and $-N(OH)COR^5$;

Z is absent or selected from a C_{5-6} carbocycle substituted with 0-3 R^b and a 5-6 membered heteroaryl comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-3 R^b;

U^a is absent or is selected from: O, NR^{a1}, C(O), $C(O)NR^{a1}$, $S(O)_p$, and $S(O)_pNR^{a1}$;

X^a is absent or selected from C_{1-4} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene

Y^a is absent or selected from O and NR^{a1};

Z^a is selected from H, a C_{5-10} carbocycle substituted with 0-3 R^c and a 5-10 membered heterocycle comprising carbon atoms and from 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-3 R^c;

provided that Z, U^a, Y^a, and Z^a do not combine to form a N-N, N-O, O-N, O-O, $S(O)_p$-O, O-$S(O)_p$ or $S(O)_p$-$S(O)_p$ group;

R^1 is selected from H, C_{1-4} alkyl, phenyl, and benzyl;

R^2 is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkenylene-Q, C_{2-6} alkynylene-Q, $(CR^aR^{a1})_{r1}C(O)(CR^aR^{a1})_r$-Q, $(CR^aR^{a1})_{r1}C(O)O(CR^aR^{a1})_r$-Q, $(CR^aR^{a2})_{r1}C(O)NR^aR^{a1}$, $(CR^aR^{a2})_{r1}C(O)NR^a(CR^aR^{a1})_r$-Q, and $(CR^aR^{a1})_{r1}S(O)_p(CR^aR^{a1})_r$-Q;

Q is selected from H, a C_{3-6} carbocycle substituted with 0-3 R^d and a 5-10 membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-3 R^d;

R^a, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

R^{a1}, at each occurrence, is independently selected from H and C_{1-4} alkyl;

R^{a2}, at each occurrence, is independently selected from C_{1-4} alkyl, phenyl, and benzyl;

R^b, at each occurrence, is independently selected from C_{1-4} alkyl, OR^a, Cl, F, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, and CF_3;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, CF_3, CH_2F, CHF_2, CF_2CH_3, $C(CH_3)_2F$, cyclopropyl, 1-methylcyclopropyl, and cyclobutyl;

alternatively, when two R^c groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-6 membered saturated ring consisting of: carbon atoms and 0-2 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, CF_3, and phenyl;

R^e, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, C_{3-10} carbocycle substituted with 0-2

R^{c1}, $(CR^aR^{a1})_{r1}$-C_{3-10} carbocycle substituted with 0-2 R^{c1}, a 5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1}, and $(CR^aR^{a1})_{r1}$-5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1};

R^5, at each occurrence, is selected from C_{1-4} alkyl substituted with 0-2 R^b, and C_{1-4} alkyl substituted with 0-2 R^f;

R^f, at each occurrence, is selected from phenyl substituted with 0-2 R^b and biphenyl substituted with 0-2 R^b;

p, at each occurrence, is selected from 0, 1, and 2;

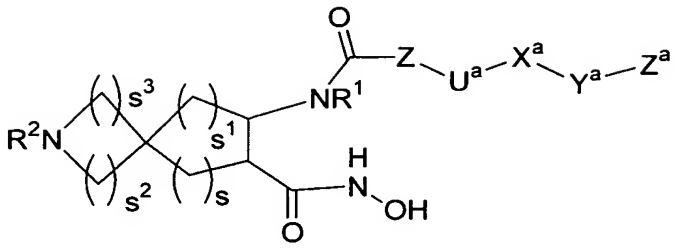
r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

r1, at each occurrence, is selected from 0, 1, 2, 3, and 4;

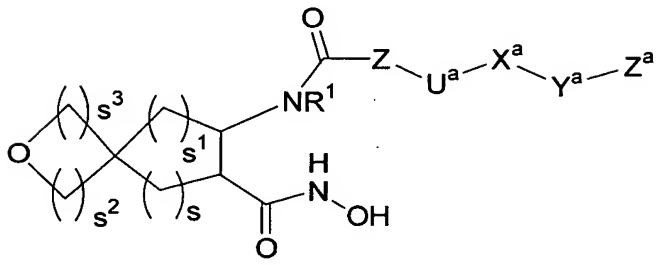
s and s^1 combine to total 2, 3, or 4; and

s^2 and s^3 combine to total 2, 3, 4, or 5.

[4] In another preferred embodiment, the present invention provides a novel compound of formula IVa or IVb:



IVa



IVb

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

Z is absent or selected from phenyl substituted with 0-3 R^b, pyridyl substituted with 0-3 R^b, thiazolyl substituted with 0-3 R^b, thienyl substituted with 0-3 R^b, and isoxazolyl substituted with 0-3 R^b;

U^a is absent or is O;

X^a is absent or is CH_2 or CH_2CH_2;

Y^a is absent or is O;

Z^a is selected from H, phenyl substituted with 0-3 R^c, and a 5-10 membered heterocycle substituted with 0-3 R^c and selected from the group: pyridyl, quinolinyl,

imidazolyl, benzimidazolyl, indolyl, 1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl, 1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl, 3,4-dihydro-2*H*-chromen-4-yl, 2*H*-chromen-4-yl, and pyrazolyl;

provided that Z, U^a, Y^a, and Z^a do not combine to form a N-N, N-O, O-N, or O-O group;

R^1 is selected from H, CH_3, and CH_2CH_3;

R^2 is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkynylene-Q, $C(O)(CR^aR^{a1})_r$-Q, $C(O)O(CR^aR^{a1})_r$-Q, $C(O)NR^a(CR^aR^{a1})_r$-Q, and $S(O)_p(CR^aR^{a1})_r$-Q;

Q is selected from H, cyclopropyl substituted with 0-1 R^d, cyclobutyl substituted with 0-1 R^d, cyclopentyl substituted with 0-1 R^d, cyclohexyl substituted with 0-1 R^d, phenyl substituted with 0-2 R^d and a heteroaryl substituted with 0-3 R^d, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;

R^a, at each occurrence, is independently selected from H, CH_3, and CH_2CH_3;

R^{a1}, at each occurrence, is independently selected from H, CH_3, and CH_2CH_3;

R^{a2}, at each occurrence, is independently selected from H, CH_3, and CH_2CH_3;

R^b, at each occurrence, is independently selected from C_{1-4} alkyl, OR^a, Cl, F, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, and CF_3;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, CF_3, CH_2F, CHF_2, CF_2CH_3, $C(CH_3)_2F$, cyclopropyl, 1-methylcyclopropyl, and cyclobutyl;

alternatively, when two R^c groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-6 membered saturated ring consisting of: carbon atoms and 0-1 heteroatoms selected from the group consisting of N, O, and $S(O)_p$;

R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, CF_3 and phenyl;

R^e, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, C_{3-10} carbocycle substituted with 0-2 R^{c1}, $(CR^aR^{a1})_{r1}$-C_{3-10} carbocycle substituted with 0-2 R^{c1}, a 5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1}, and $(CR^aR^{a1})_{r1}$-5-14 membered heterocycle

comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1};

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

r1, at each occurrence, is selected from 0, 1, 2, and 3;

s and s^1 combine to total 2, 3, or 4; and

s^2 and s^3 combine to total 2, 3, 4, or 5.

[5] In another preferred embodiment, the present invention provides a novel compound of formula IVa or IVb, wherein;

Z is absent or selected from phenyl substituted with 0-3 R^b and pyridyl substituted with 0-3 R^b;

U^a is absent or is O;

X^a is absent or is CH_2 or CH_2CH_2;

Y^a is absent or is O;

Z^a is selected from H, phenyl substituted with 0-3 R^c, pyridyl substituted with 0-3 R^c, and quinolinyl substituted with 0-3 R^c;

provided that Z, U^a, Y^a, and Z^a do not combine to form a N-N, N-O, O-N, or O-O group;

R^1 is selected from H, CH_3, and CH_2CH_3;

R^2 is selected from Q, C_{1-6} alkylene-Q, C_{2-6} alkynylene-Q, $C(O)(CR^aR^{a1})_r$-Q, $C(O)O(CR^aR^{a1})_r$-Q, $C(O)NR^a(CR^aR^{a1})_r$-Q, and $S(O)_p(CR^aR^{a1})_r$-Q;

Q is selected from H, cyclopropyl substituted with 0-1 R^d, cyclobutyl substituted with 0-1 R^d, cyclopentyl substituted with 0-1 R^d, cyclohexyl substituted with 0-1 R^d, phenyl substituted with 0-2 R^d and a heteroaryl substituted with 0-3 R^d, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;

R^a, at each occurrence, is independently selected from H, CH_3, and CH_2CH_3;

R^{a1}, at each occurrence, is independently selected from H, CH_3, and CH_2CH_3;

R^{a2}, at each occurrence, is independently selected from H, CH_3, and CH_2CH_3;

R^b, at each occurrence, is independently selected from C_{1-4} alkyl, OR^a, Cl, F, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, and CF_3;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, and CF_3;

R^d, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, =O, NR^aR^{a1}, $C(O)R^a$, $C(O)NR^aR^{a1}$, $S(O)_2NR^aR^{a1}$, $S(O)_pR^{a2}$, CF_3 and phenyl;

R^e, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, -CN, NO_2, NR^aR^{a1}, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a1}$, $R^aNC(O)NR^aR^{a1}$, $OC(O)NR^aR^{a1}$, $R^aNC(O)OR^a$, $S(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $NR^aS(O)_2NR^aR^{a1}$, $OS(O)_2NR^aR^{a1}$, $NR^aS(O)_2R^{a2}$, $S(O)_pR^{a2}$, CF_3, CF_2CF_3, C_{3-10} carbocycle substituted with 0-2 R^{c1}, $(CR^aR^{a1})_{r1}$-C_{3-10} carbocycle substituted with 0-2 R^{c1}, a 5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1}, and $(CR^aR^{a1})_{r1}$-5-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ and substituted with 0-2 R^{c1};

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

r1, at each occurrence, is selected from 0, 1, 2, and 3;

s and s^1 combine to total 2, 3, or 4; and

s^2 and s^3 combine to total 2, 3, 4, or 5.

[6] In another preferred embodiment, the present invention provides a novel compound of formula IVa or IVb, wherein;

Z is phenyl, thiazolyl, thienyl or isoxazolyl;

U^a is absent or is O;

X^a is absent or is CH_2 or CH_2CH_2;

Y^a is absent or is O;

Z^a is a 5-10 membered heterocycle substituted with 0-2 R^c and selected from the group: 4-pyridyl, 4-quinolinyl, 1*H*-benzimidazol-1-yl, 1*H*-indol-1-yl, and 1*H*-indol-3-yl, 1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl;

R^1 is H;

R^c, at each occurrence, is independently selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, CF_3, CHF_2, CH_2F, CF_2CH_3, $C(CH_3)_2F$, NH_2, $NH(CH_3)$, $N(CH_3)_2$, cyclopropyl, 1-methylcyclopropyl, and cyclobutyl;

s and s^1 combine to total 2, 3, or 4; and

s^2 and s^3 combine to total 2, 3, 4, or 5.

[7] In another preferred embodiment, the present invention provides a compound selected from the group:

(7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1,4-dioxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*S*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(2*S*,3*R*)-*N*-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-6,10-dioxaspiro[4.5]decane-2-carboxamide;

(7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1,4-dithiaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-{[4-(2-butynyloxy)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-isopropyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-1*H*-indol-3-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-[(4-{[2-(difluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2-cyclopropyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2-cyclobutyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-isopropyl-1*H*-imidazol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-1*H*-indol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(1-methylcyclopropyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-[(4-{[2-(fluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-[(4-{[2-(1-fluoro-1-methylethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-{[4-(1*H*-indol-3-ylmethyl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-[(4-{[2-(1,1-difluoroethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2,3-dimethyl-1*H*-indol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2-ethyl-1*H*-indol-3-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(trifluoromethyl)-1*H*-indol-1-yl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-{[4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-{[4-(3,4-dihydro-2*H*-chromen-4-yl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-{[4-(2*H*-chromen-4-yl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

N-{(5*R*,7*R*,8*S*)-8-[(hydroxyamino)carbonyl]-1-oxaspiro[4.4]non-7-yl}-2-[(2-isopropyl-1*H*-benzimidazol-1-yl)methyl]-1,3-thiazole-4-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(3,5-dimethyl-1*H*-pyrazol-4-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2,2-dimethyl-1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(trifluoromethyl)-4-quinolinyl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2-ethyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-isopropyl-4-quinolinyl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(5*R*,7*S*,8*R*)-8-[(4-{[2-(dimethylamino)-4-quinolinyl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2-cyclopropyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-{[4-(1,3-dihydrofuro[3,4-*b*]quinolin-9-ylmethyl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2,3-dimethyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-methyl-8-(trifluoromethyl)-4-quinolinyl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(3-ethyl-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(2,6-dimethyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(6-chloro-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(6-fluoro-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

(5*R*,7*S*,8*R*)-8-({4-[(7-chloro-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide; and

(5*R*,7*S*,8*R*)-8-({4-[(2,6-dimethyl-4-pyridinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide;

or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method for treating or preventing an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

In another embodiment, the present invention provides a novel method of treating a disease or condition, wherein the disease or condition is referred to as acute infection, acute phase response, age related macular degeneration, alcoholism, allergy, allergic asthma, anorexia, aneurism, aortic aneurism, asthma, atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation,

intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pulmonary emphysema, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

In another embodiment, the present invention provides novel compounds of the present invention for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of the present invention for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

This invention also encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional even more preferred embodiments of the present invention. It is also understood that each and every element of any embodiment

is intended to be a separate specific embodiment. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, 800, 850, or 900 grams per mole. More preferably, the molecular weight is less than about 850 grams per mole. Even more preferably, the molecular weight is less than about 750 grams per mole. Still more preferably, the molecular weight is less than about 700 grams per mole.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

The term "independently selected from", "independently, at each occurrence" or similar language, means that the labeled R substitution group may appear more than once and that each appearance may be a different atom or molecule found in the definition of that labeled R substitution group. Thus if the labeled R^a substitution group appear four times in a given permutation of Formula I, then each of those labeled R^a substitution groups may be a different group falling in the definition of R^a. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via

which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-10} alkyl (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v=1 to 3 and w=1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. C_{1-10} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl, is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any

stable point along the chain, such as ethenyl and propenyl. C_{2-10} alkenyl (or alkenylene), is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkenyl groups. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-10} alkynyl (or alkynylene), is intended to include C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is

fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heterotams independently selected from the group consisting of N, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl,

naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl, 1,1-dioxido-2,3-dihydro-4H-1,4-benzothiazin-4-yl, 1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl, and 3,4-dihydro-2*H*-chromen-4-yl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base

salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form.

Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit a desired metalloprotease in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*, 27-55, occurs when the effect (in this case, inhibition of the desired target) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased increased anti-inflammatory effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

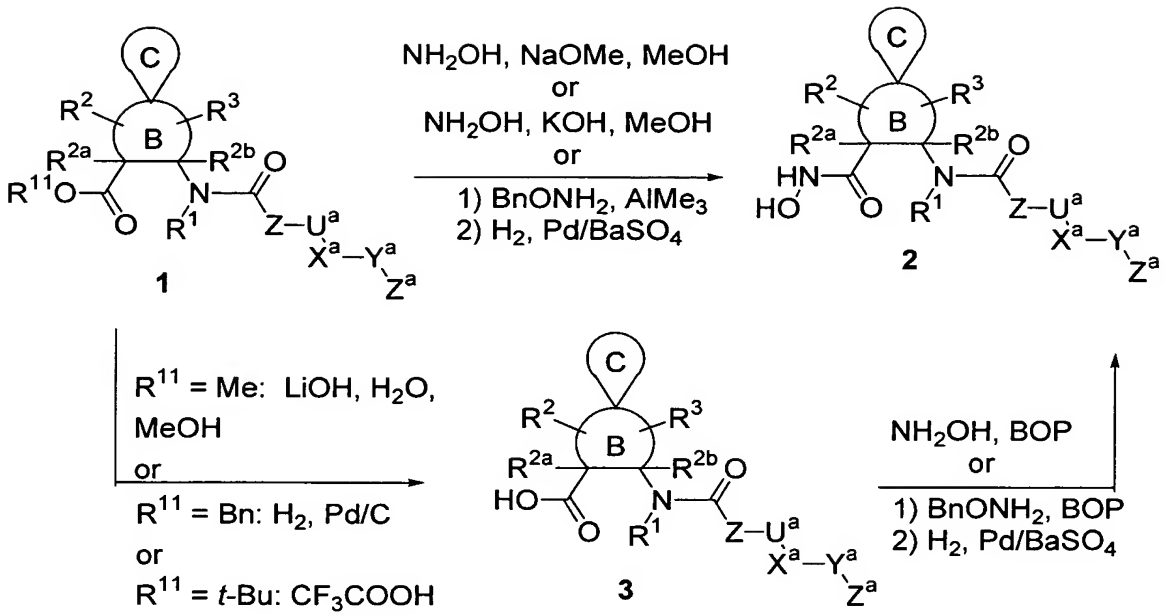
The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods

described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

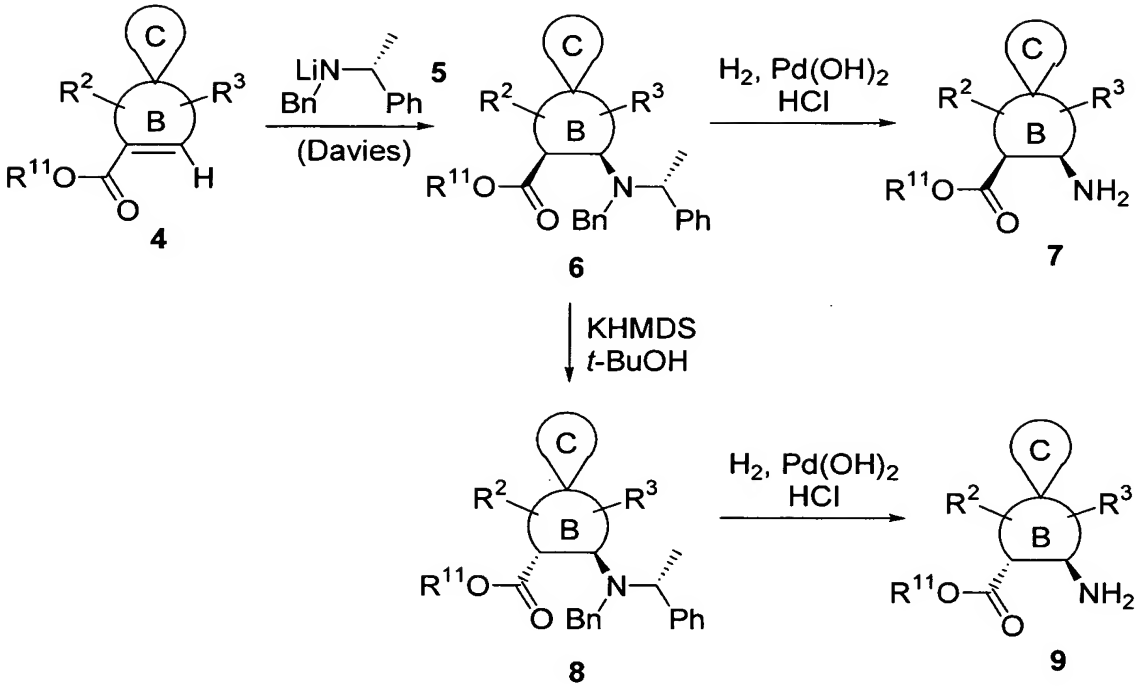
A variety of compounds of formula (I) wherein A is hydroxamic acid group are prepared from the corresponding esters via several routes known in the literature (Scheme 1). The methyl ester of **1** (R^{11} = Me) is directly converted to hydroxamic acid **2** by treatment with hydroxylamine under basic conditions such as KOH or NaOMe in solvents such as methanol. The methyl ester of **1** (R^{11} = Me) can also be converted to O-benzyl protected hydroxamic acid with O-benzylhydroxylamine under similar conditions or using Weinreb's trimethylaluminum conditions (Levin, J. I.; Turos, E.; Weinreb, S. M. *Syn. Commun.* **1982**, *12*, 989) or Roskamp's bis[bis(trimethylsilyl)amido]tin reagent (Wang, W.-B.; Roskamp, E. J. *J. Org. Chem.* **1992**, *57*, 6101). The benzyl ether is removed by methods well known in the literature such as hydrogenation using palladium on barium sulfate in hydrogen, to give compound **2**. Alternatively, **2** can be prepared through the carboxylic intermediate **3**. Carboxylic acid **3** is converted to **2** via coupling with hydroxylamine, or O-benzylhydroxylamine followed by deprotection.

Scheme 1



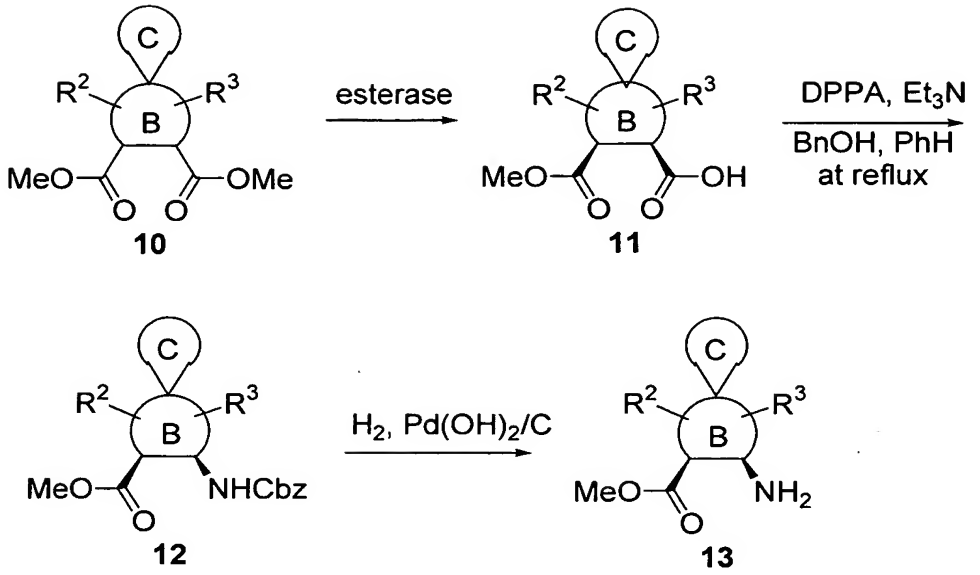
The β-amino acid moiety in formula (I) can be synthesized following a variety of literature routes as reviewed in "Enantioselective Synthesis of β-Amino Acids" (E. Juaristi, Ed. Wiley-VCH, 1997). One representative approach using Davies protocol is summarized in Scheme 2 (*J. Chem. Soc. Perkin Trans I*, **1994**, 1411). Michael addition of lithium amide **5** to **4** gives cis product **6**. The stereochemical configuration of **6** is governed by the chirality of **5**. De-benzylation of **6** provides cis-β-amino acid **7**. The trans-β-amino acid **9** can be prepared by epimerization of **6** followed by de-benzylation. Since both amine enantiomers of **5** are commercially available, this approach provides ready access to both cis and trans isomers (**7** and **9**), as well as their antipodes.

Scheme 2



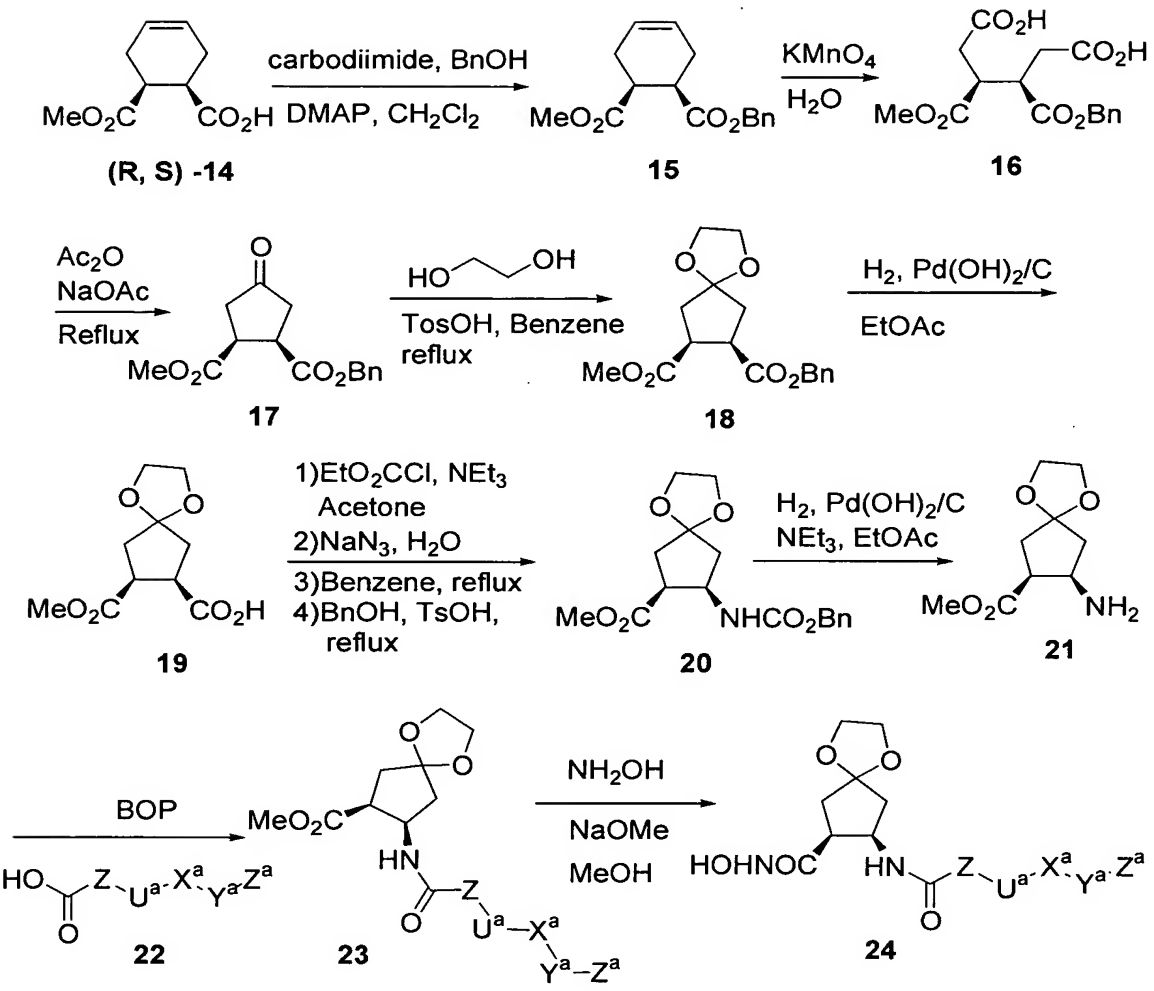
Alternatively, these β-amino acids can be prepared from the corresponding dicarboxylate derivatives (Scheme 3). The dicarboxylate derivatives can be de-symmetrized through enzymatic resolution (for an example with lipase, see Gais, H.-J. et al, *J. Am. Chem. Soc.* **1989**, *54*, 5115), or through chemical resolution (for an example with TADOLates, see Seebach, D. et al. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2395). The optically pure mono-ester **11** is converted to Cbz protected β-amino acid ester **12** through Curtius rearrangement (for a related example, see Kobayashi, S. et al. *Tetrahedron Lett.* **1984**, *25*, 2557). Removal of Cbz protecting group provides cis-amino acid ester **13**. The corresponding trans analogue of **13** can be prepared from the ester of trans di-carboxylic acid of **10** following same sequence.

Scheme 3



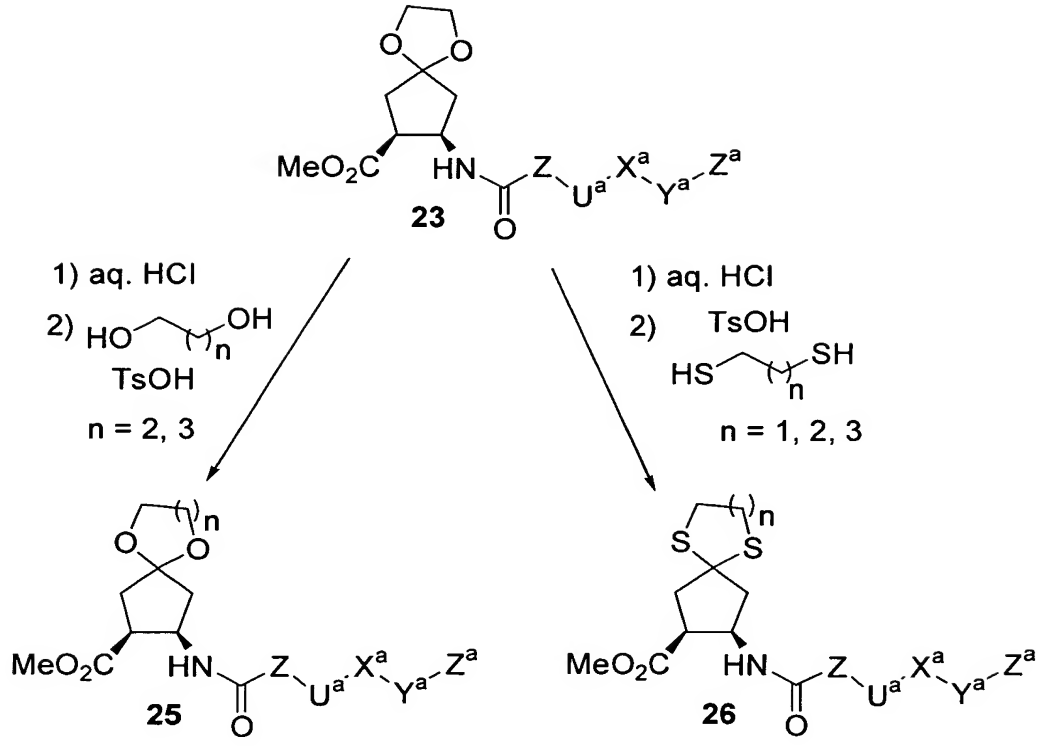
A series of compounds of formula (I) wherein ring B is a cyclopentane and ring C is a dioxolane are prepared following the sequence outlined in Scheme 4. The acid of compound **14** can be protected as the benzyl ester and the cyclohexene **15** is oxidized to the bis-acid and cyclized to the ketone **17** (for a related example see: Gais et al. *J. Org. Chem.* **1989**, *54*, 5115). The ketone is converted to the ethylene ketal **18**. Protecting group manipulations and Curtius rearrangement (for a related example, see Kobayashi, S. et al, *Tetrahedron Lett.* **1984**, *25*, 2557) give intermediate **20**. Hydrogenolysis gives amino acid ester **21**. **21** is coupled with acid **22** to provide **23**. Which is converted to the hydroxamic acid **24**.

Scheme 4



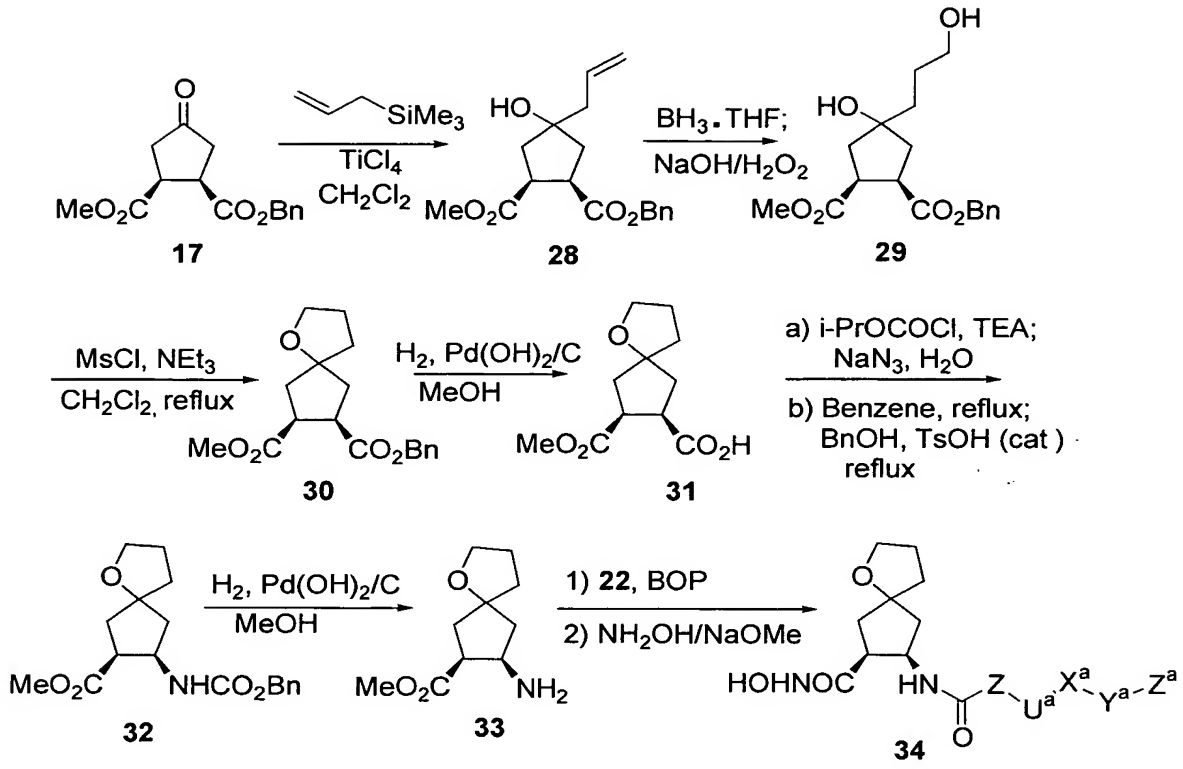
A series of compounds of formula (I) wherein ring B is cyclopentane and ring C is a dioxane, dioxepane, dithialane, dithiane, or dithiepane are prepared following the sequence outlined in Scheme 5. The ethylene ketal **23** deketalized with HCl and the resultant ketone reketalized with the appropriate diol or thiol to give **25** and **26** respectively, which can be converted as previously described to the desired hydroxamic acid.

Scheme 5



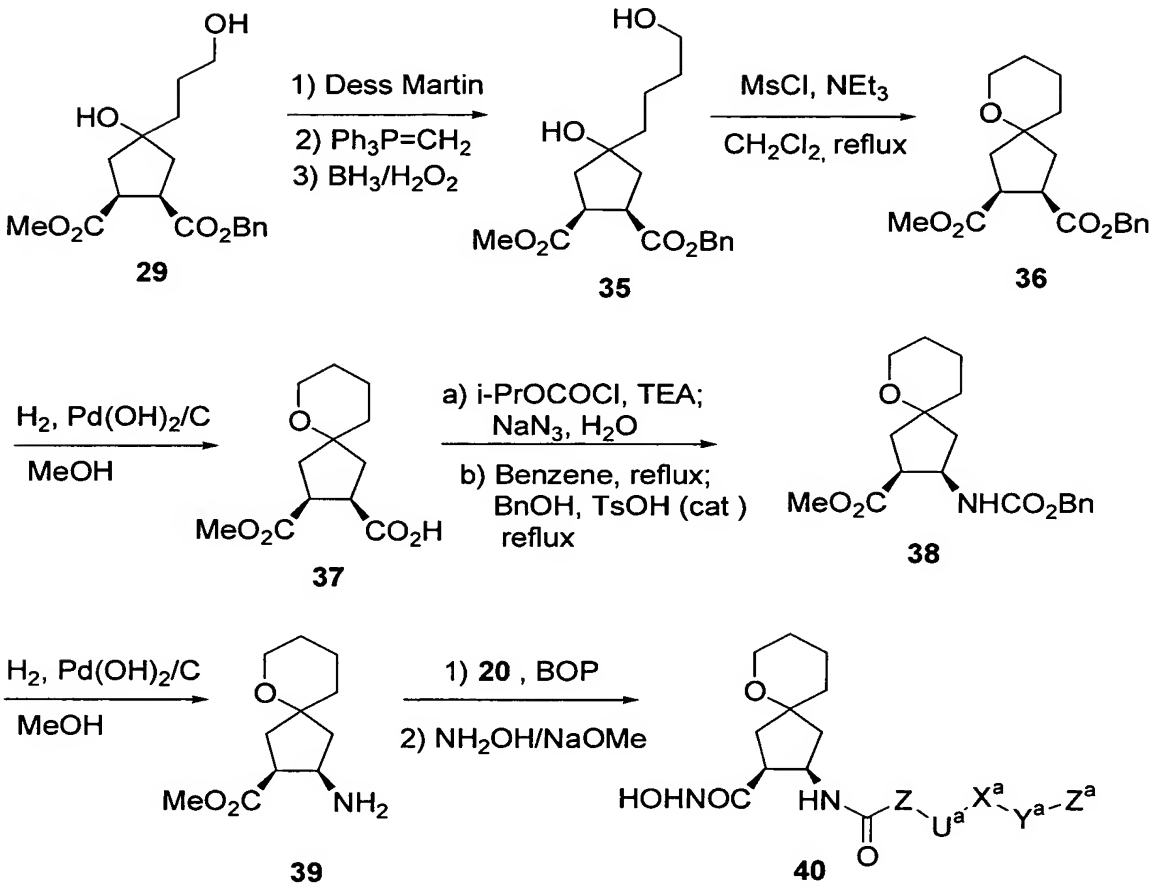
A series of compounds of formula (I) wherein ring B is cyclopentane and ring C is a tetrahydrofuran are prepared following the sequence outlined in Scheme 6. Ketone **17** is treated with allyltrimethylsilane in the presence of titanium tetrachloride to give **28**, hydroboration/oxidation yields the primary alcohol which is cyclized to the the tetrahydrofuran **30**. Conversion of **30** to the desired amine **33** and then amide and finally hydroxamic acid **34** proceeds through the steps as previously described.

Scheme 6



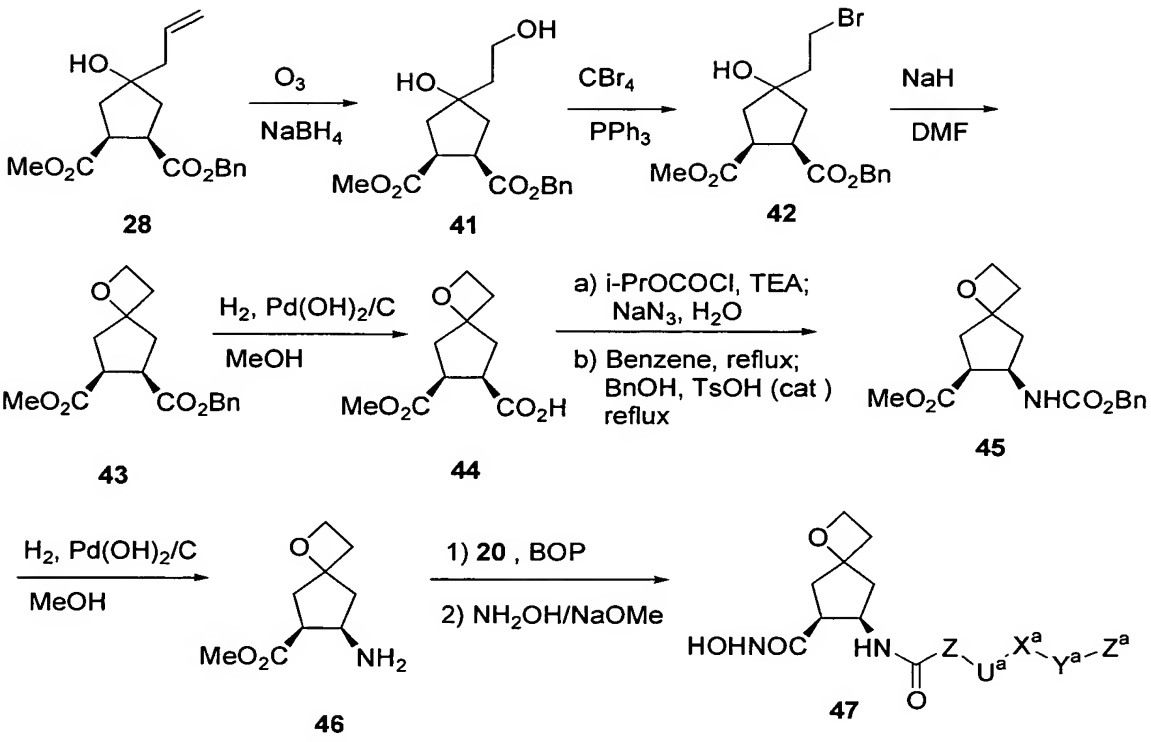
A series of compounds of formula (I) wherein ring B is cyclopentane and ring C is a tetrahydropyran are prepared following the sequence outlined in Scheme 7. Alcohol **29** is oxidized and converted to the olefin using methylene trphenylphosphorane followed by a hydroboration/oxidation sequence to deliver diol **35**. Cyclization followed by a similar sequece as described earlier delivers **40**.

Scheme 7



A series of compounds of formula (I) wherein ring B is cyclopentane and ring C is an oxetane are prepared following the sequence outlined in Scheme 8. Olefin **28** is ozonized and reduced the diol **41**. Conversion to the primary bromide followed by cycliztion (NaH, DMF) delivers the oxetane **43**. Following a similar sequence as described earlier delivers **47**.

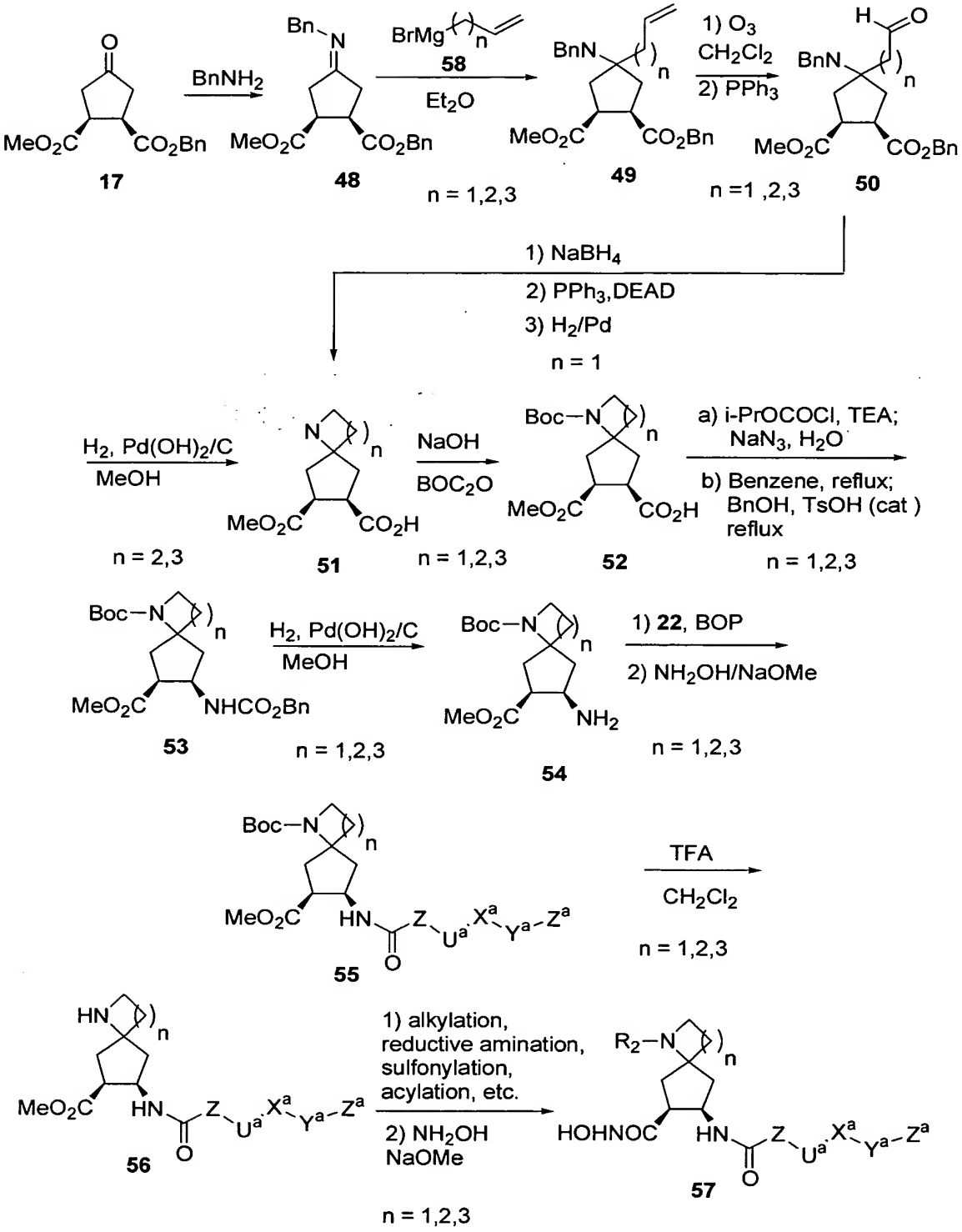
Scheme 8



A series of compounds of formula (I) wherein ring B is a cyclopentane and ring C is an azetidine, pyrrolidine or a piperidine are prepared following the sequence outlined in Scheme 9. The benzylimine of ketone **17** is treated with Grignard reagent **58** (for a related example see: Berthe et. al. *Tetrahedron Letters*, **1997**, *38*, 1393-1396). The olefin **49** is then oxidized to the aldehyde **50**. For azetidine formation (n=1) aldehyde **50** is reduced to the alcohol and cyclized using Mitsunobu conditions (for azetidine formation of benzyl amines using Mitsunobu conditions, see: Sammes and Smith, *J. Chem. Soc. Chem Commun*. **1983**, 682). For pyrrolidine and piperidine formation (n = 5,6), the aldehyde is converted to the desired ring by hydrogenolysis (for formation of 5 or 6-membered rings by reductive amination, see: Lubell, et al: *J. Org. Chem*. **1996**, *61*, 9447 and Watanabe, et al:

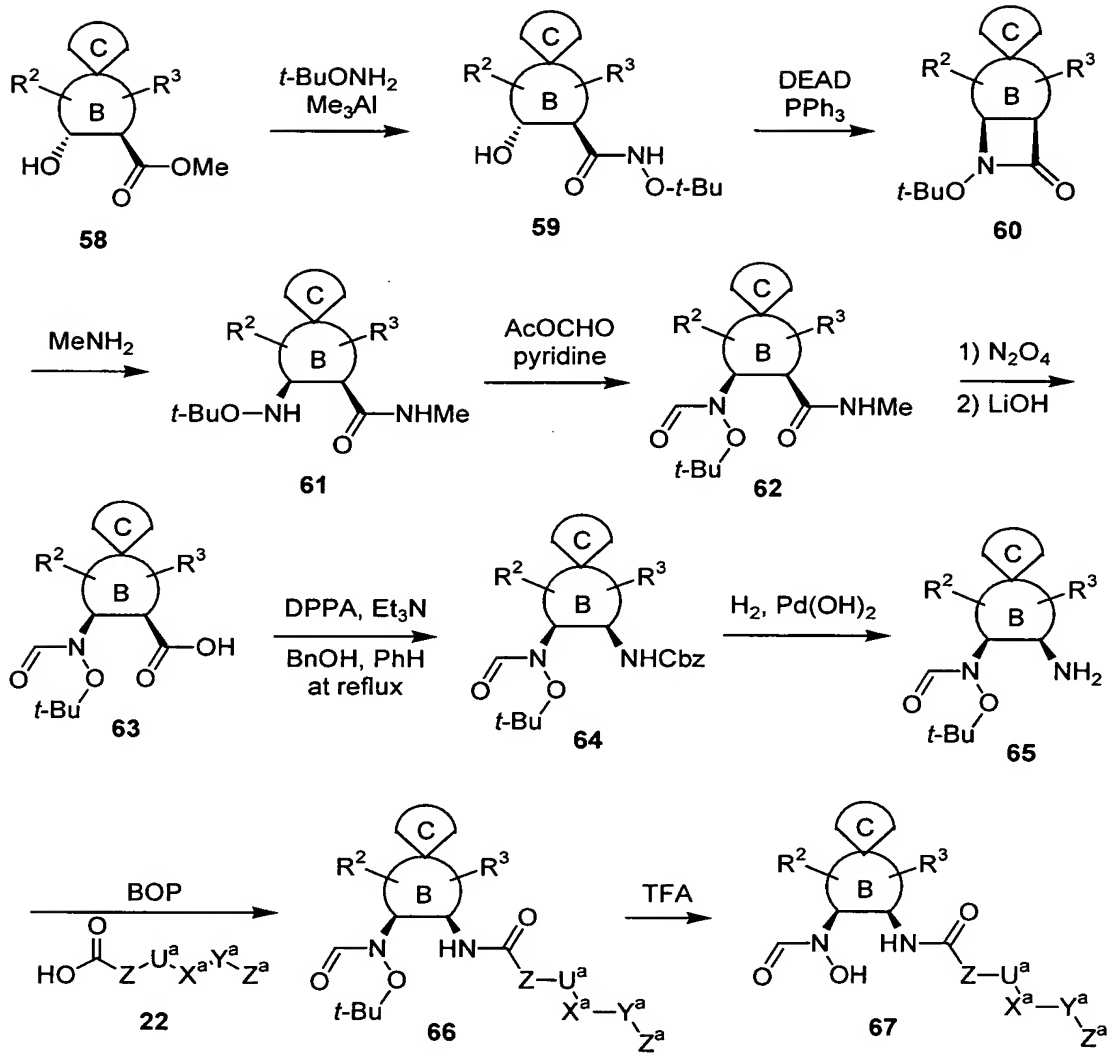
J.Org. Chem, **1989**, *54*, 4088). Appropriate protection of the nitrogen is followed by conversion of the acid to a protected amine through a Curtius rearrangement to give **53** . Protecting group manipulation and coupling to **22** yields **55**. The BOC protecting group can be removed (TFA) and the nitrogen functionalized by amidation, alkylation, reductive amination, sulfonylation , etc. Conversion to the hydroxamate **57** proceeds as previously described.

Scheme 9


BnNH2
BrMg
58
Et2O
1) O3
CH2Cl2
2) PPh3
17
48
n = 1,2,3
49
n =1 ,2,3
50
1) NaBH4
2) PPh3,DEAD
3) H2/Pd
n = 1
H2, Pd(OH)2/C
MeOH
n = 2,3
51
NaOH
BOC2O
n = 1,2,3
52
a) i-PrOCOCl, TEA;
NaN3, H2O
b) Benzene, reflux;
BnOH, TsOH (cat)
reflux
n = 1,2,3
53
n = 1,2,3
54
1) 22, BOP
2) NH2OH/NaOMe
n = 1,2,3
55
TFA
CH2Cl2
n = 1,2,3
56
1) alkylation,
reductive amination,
sulfonylation,
acylation, etc.
2) NH2OH
NaOMe
n = 1,2,3
57

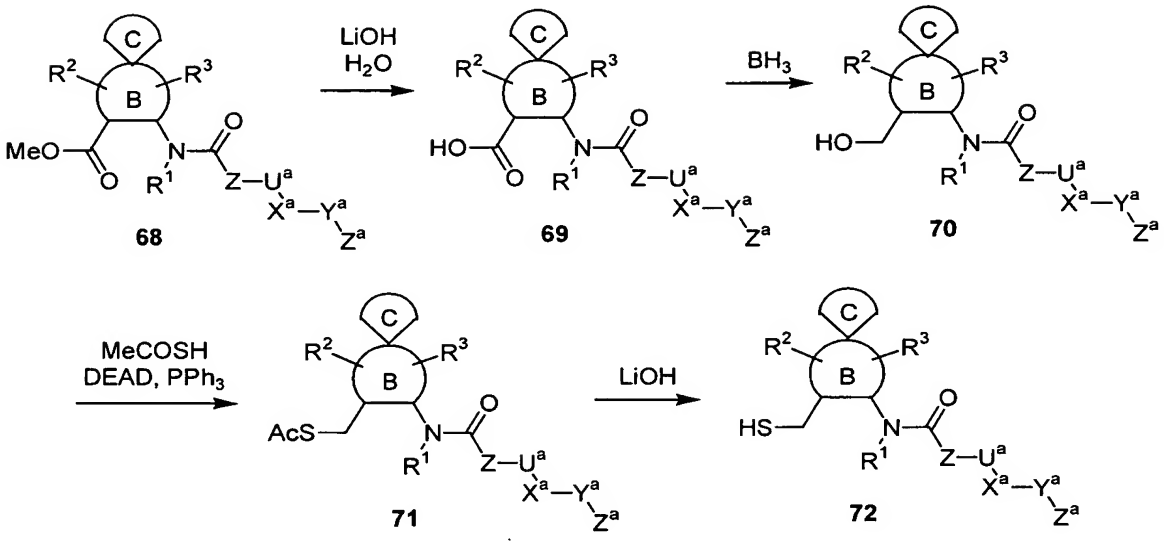
A series of compounds of formula (I) wherein A is N-formylhydroxylamino group are prepared following the sequence outlined in Scheme 10. Starting from *trans*-hydroxy ester **58**, Wenreib or Roskamp amide formation with *O*-*t*-butylhydroxylamine gives **59** (Levin, J. I.; Turos, E.; Weinreb, S. M. *Syn. Commun.* **1982**, *12*, 989 and Wang, W.-B.; Roskamp, E. J. *J. Org. Chem.* **1992**, *57*, 6101). β-Lactam is formed under Mitsunobu conditions (Mitsunobu, O. *Synthesis*, **1981**, 1). Opening of lactam **60** with methylamine followed by N-formylation provide **62**. The N-methyl amide moiety of **62** is converted to carboxylic acid by nitrosation with N2O4 or NaNO2, and hydrolysis with LiOOH (Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535). Acid **63** is converted to **66** as described previously. Acid hydrolysis of *t*-Butyl group in **66** completes the synthesis.

Scheme 10



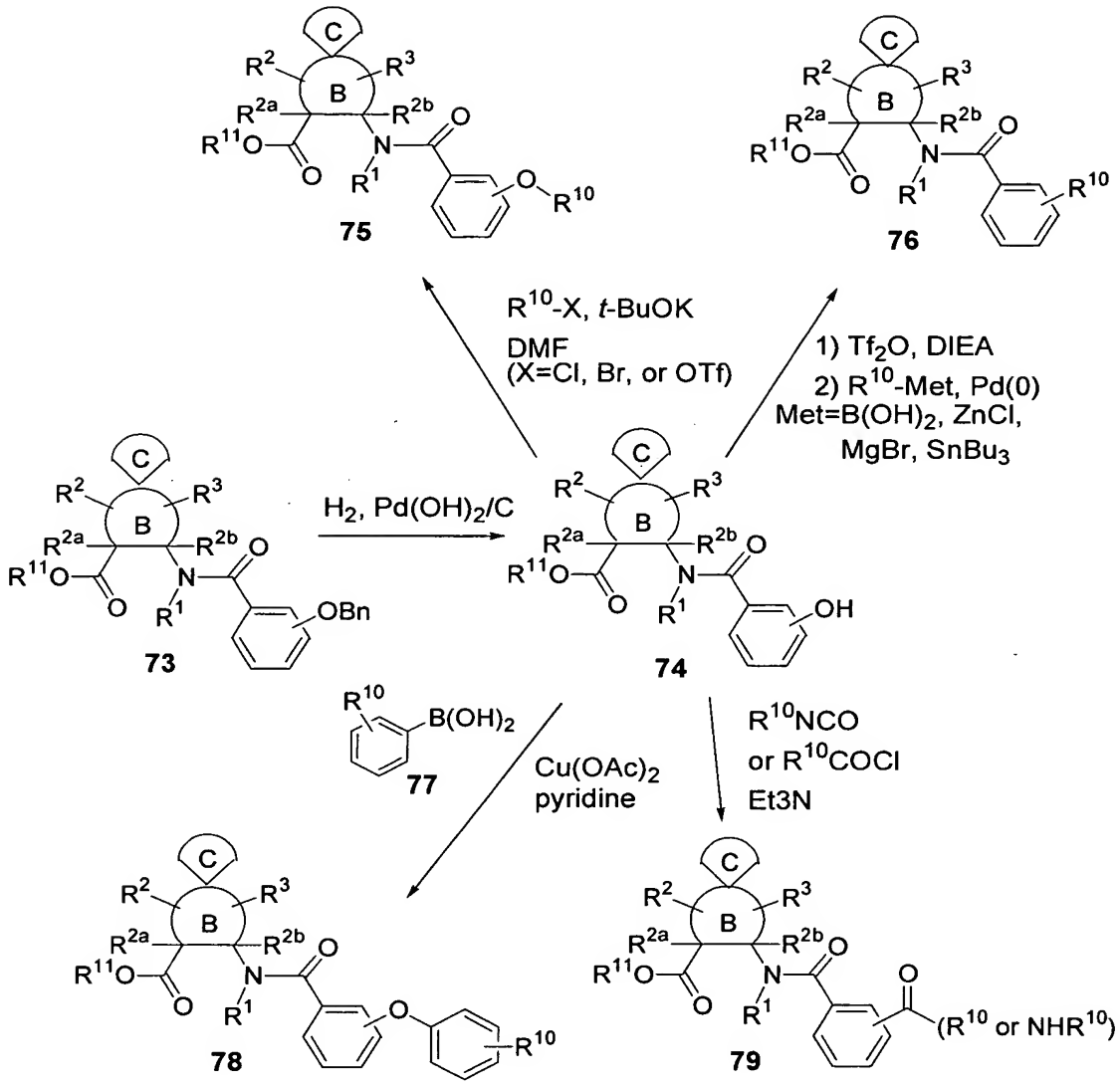
A series of compounds of formula (I) wherein A is mercaptomethyl group are prepared following the sequence outlined in Scheme 11. Saponification and hydroboration of **68** give alcohol **70**. Mitsunobu reaction with thioacetic acid followed by lithium hydroxide hydrolysis provides the desired thiol **72**.

Scheme 11



A variety of compounds of formula (I) wherein $Z\text{-}U^a\text{-}X^a\text{-}Y^a\text{-}Z^a$ is a functionalized phenyl group can be prepared by methods described in Scheme 12. Intermediate **73**, available from schemes described previously, is converted to phenol **74** by hydrogenolysis. Phenol **74** is used as common intermediates for structure diversification. Reaction of **74** with R^{10}-X provides **75**, an alternative is the reaction of **74** with R^{10}-OH under Mitsunobu conditions to produce **75**. R^{10} can be appended directly to the aromatic ring by converting **74** to an aryl triflate then reaction with an organometallic in the presence of a palladium (0) catalyst to give **76**. **74** can also be reacted with acyl halides or isocyanates to afford **79**. Biaryl ethers **78** can be produced by treatment of **74** with aryl boronic acids in the presence of a copper catalyst. Esters **74-76** and **78-79** are converted to the hydroxamic acids following the sequences outlined in Scheme 1.

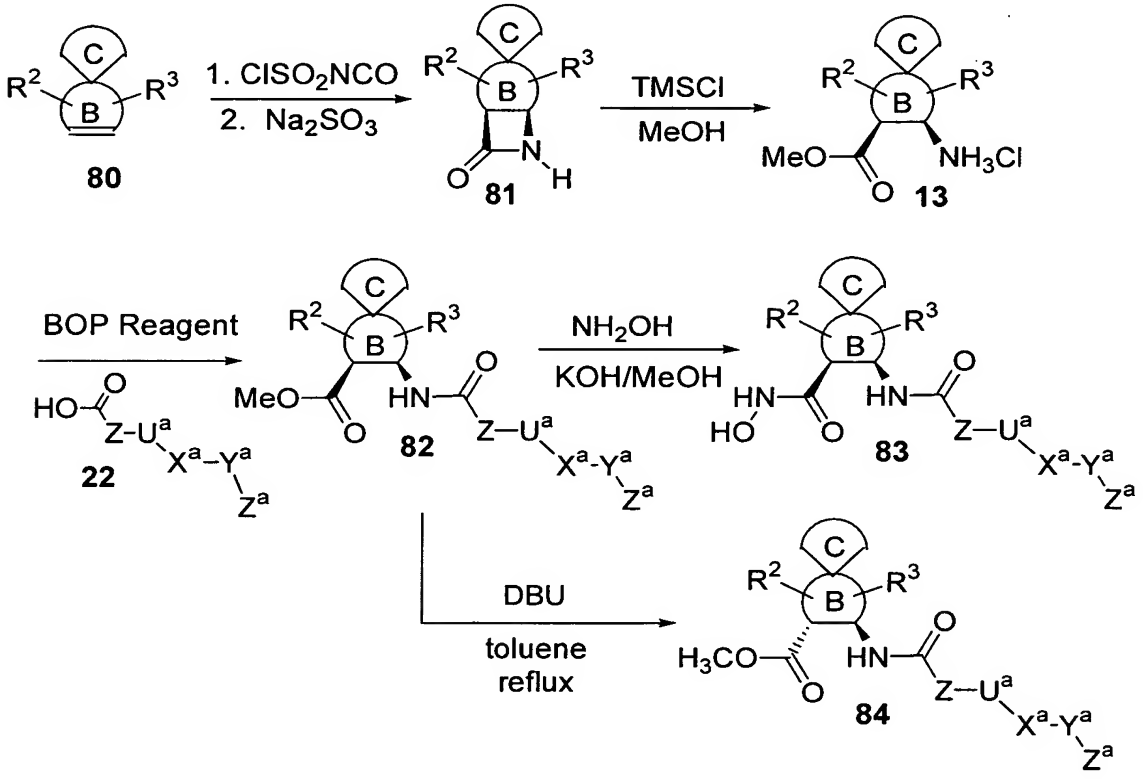
Scheme 12



Another procedure for the synthesis of cyclic β-amino acids useful for the preparation of compounds of formula I uses the well documented [2+2] cycloaddition of chlorosulfonylisocyanate with olefins (Scheme 13, Dhar, D.N.; Murthy, K.S.K. *Synthesis* **1986**, 437-449). When **80** is reacted with chlorosulfonylisocyanate the resulting β-lactam intermediate **81** can be opened to afford cyclic β-amino acids using a variety of conditions, but most conveniently with chlorotrimethylsilane/methanol. The

methyl ester **13** can then be converted to compounds of formula I followed our usual procedure of attaching carboxcylic acid **20** to provide **82** then hydroxamic acid **83** is formed by our standard conditions. The *trans* β-amino acids **84** are available by equilibration of *cis* amide ester **82** under basic conditions.

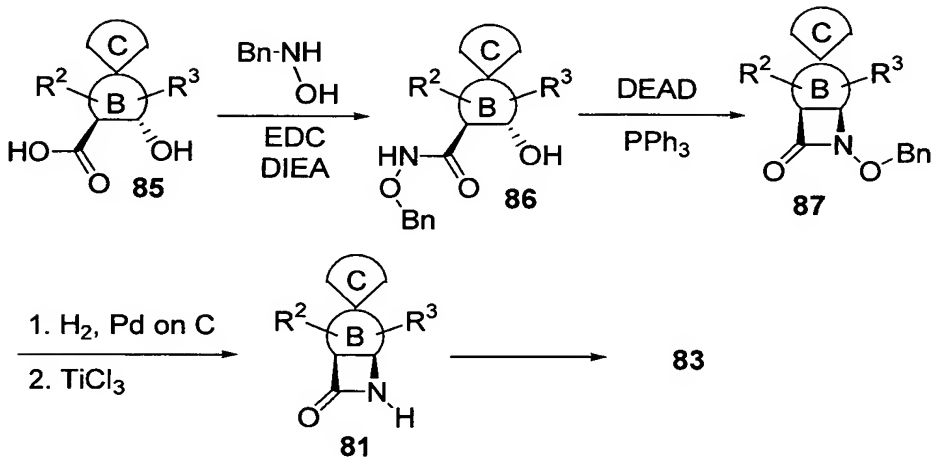
Scheme 13



An alternative synthesis of **83** begins with formation of benzyl hydroxamate **86** from *trans* β-hydroxy carboxylate **85** (Scheme 14). Intramolecular cyclization of **86** under Mitsunobu conditions (Bellettini, J.R.; Miller, M.J. Tetrahedron Letters **1997**, *38*, 167-168) then affords benzyl protected hydroxy β-lactam **87**. Removal of the benzyl group by hydrogenolysis and reduction of the

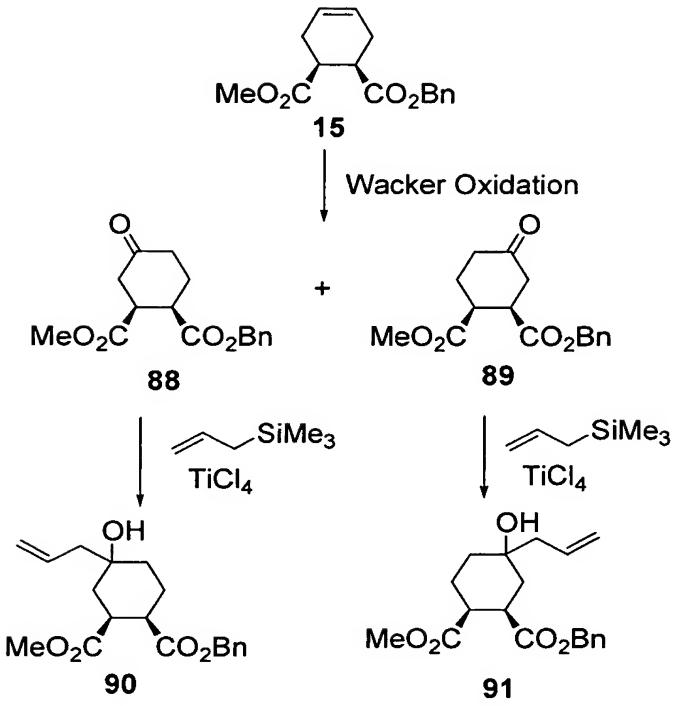
intermediate N-hydroxy β-lactam provides **81**, which can be converted to final products as shown in the previous scheme.

Scheme 14



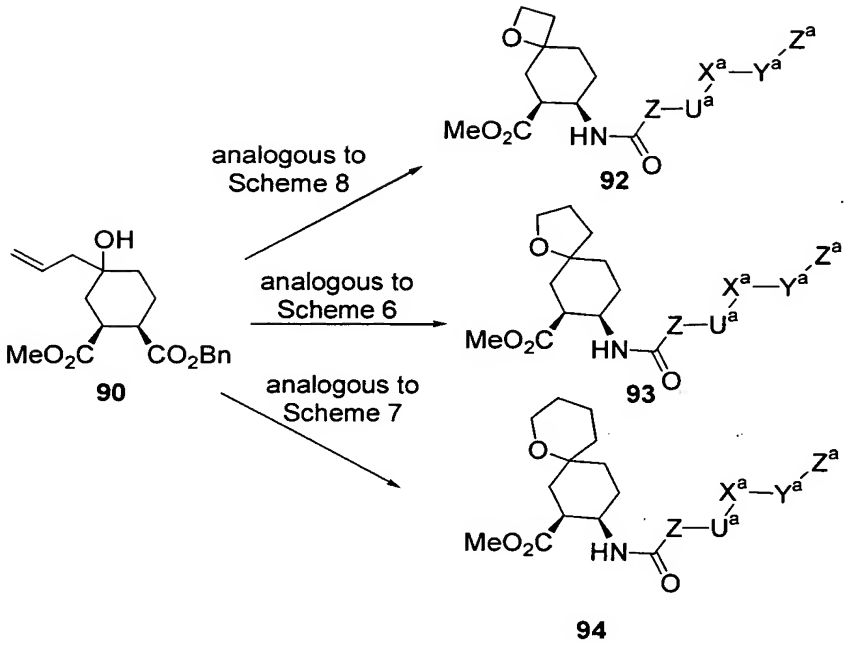
Outlined in Scheme 15 are compounds of Formula I wherein ring B is a cyclohexane. The regioisomeric ketones **88** and **89** are available from **15** via Wacker oxidation. The alcohols **90** and **91** are then available from previously described methods.

Scheme 15

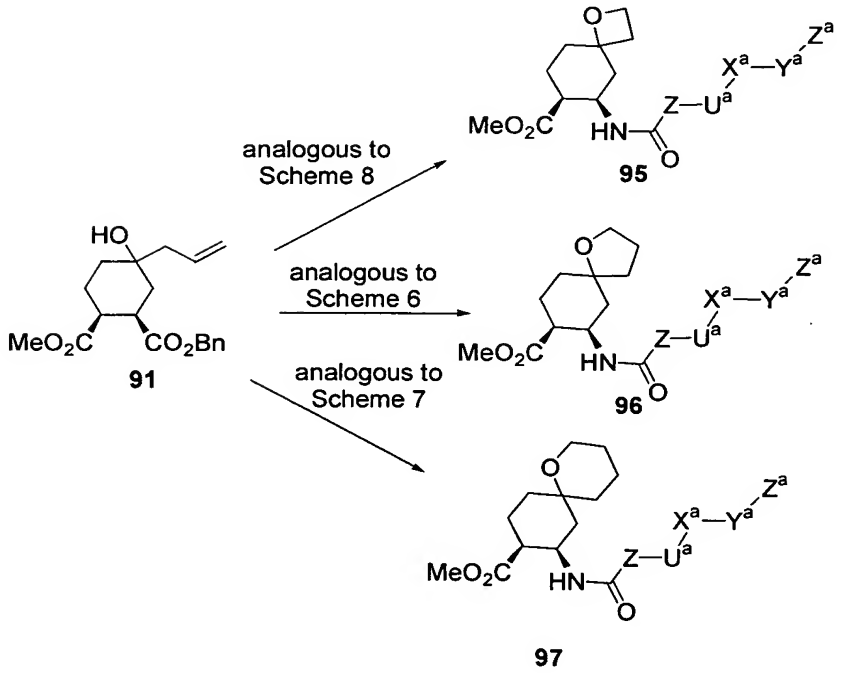


Alcohols **90** (Scheme 16) and **91** (Scheme 17) can then be converted to 4-, 5-, and 6-membered spirocyclic ethers following chemistry that was outlined in the previously noted schemes.

Scheme 16

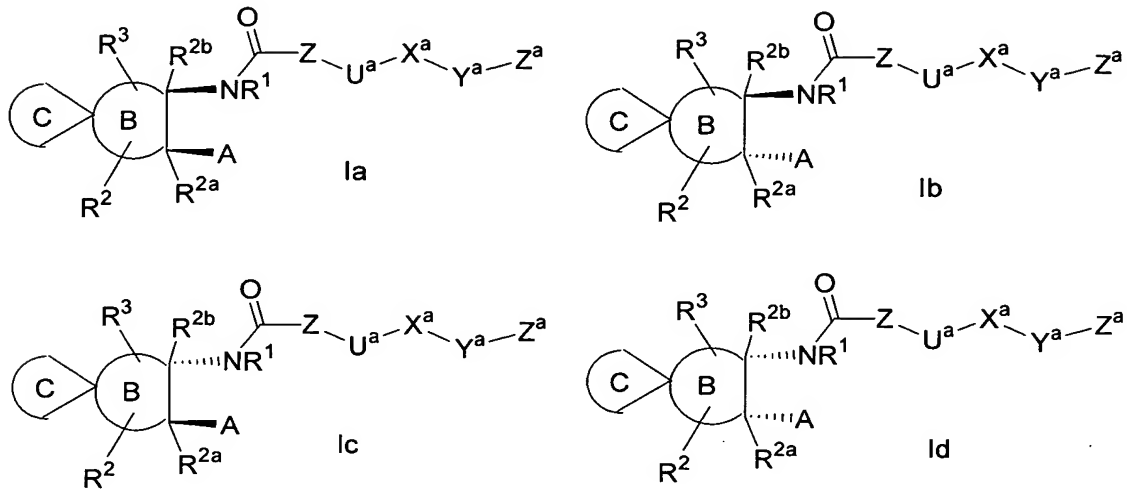


Scheme 17



One diastereomer of a compound of Formula I may display superior activity compared with the others.

Thus, the following stereochemistries are considered to be a part of the present invention.



When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al. *Antimicrobial Agents and Chemotheraphy,* **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al. *Tetrahedron Lett.* **1995**, *36*, 8937-8940.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or

milligrams, "mL" for milliliter or milliliters, "^{1}H" for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

(7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1,4-dioxaspiro[4.4]nonane-7-carboxamide

(1a) 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (73.0g, 1.5eq) was added to a mixture of (1S,2R)-1-methyl cis-1,2,3,6-tetrahydrophthalate (46.8 g, 254.2 mmol), benzyl alcohol (30.2 g, 1.1 eq) and 4-dimethylaminopyridine (3.0 g, 0.1 eq) in dichloromethane (470 mL) at 0 °C and let warm to room temperature. After 3 h, the solution was cooled to 0 °C and 1N HCl (300 mL) was added. The mixture was extracted with dichloromethene (2 X 300 mL). The organic layer was washed successively with brine (200 mL), dried ($MgSO_4$) and concentrated. The crude product (70 g) was purified by silica gel column chromatography (ethyl acetate-hexane, 1:10). The desired compound was obtained as colorless oil (68.8 g, 99%). MS found: $(M+H)^+$ = 275.

(1b) The olefin from reaction (1a) (68.8 g, 251 mmol) was added dropwise to a solution of potassium permanganate (125 g, 3.2 eq) in water (400 mL) at 0 °C. After 20 min stirring at 0 °C, TLC showed the presence of starting olefin. Another portion of water (400 mL) and potassium

permanganate (125 g) were added. After 20 min the reaction was complete (by TLC). Sulfur dioxide was bubbled through the mixture at 0 °C until the color of the solution turned pink from purple (2 h). The mixture was filtered and the filtrate was acidified by adding concentrated HCl to pH = 1. The reaction was extracted with ethyl acetate (5 X 500 mL) and the combined organic layers were dried over sodium sulfate. After filtration and concentration, the target diacid was obtained (74 g, 87% yield) and taken on without further purification. MS found $(M+H)^+$ = 339.

(1c) Sodium acetate (11.4 g, 138 mmol) was added to a solution of the dicarboxylic acid from reaction (1b) (57 g, 169 mmol) in acetic anhydride (43 g, 421 mmol) at rt. The reaction was refluxed for 2h, and cooled to rt. Acetic anhydride was removed by rotary evaporation under reduced pressure. Water (600 mL) was added and the residue was extracted with ethyl acetate (1 L X 2). The combined organic layers were dried over $MgSO_4$. After filtration and concentration, the crude ketone was obtained. Purification by silica gel column chromatography (Ethyl acetate 33% in hexane) furnished the target ketone (21 g, 45% yield). MS found: $(M)^+$ = 276.

(1d) The ketone from reaction (1c)(7g, 25.3 mmol), ethylene glycol (15.7 g, 253.3 mmol) and p-toluenesulfonic acid monohydrate (481 mg, 2.5 mmol) were refluxed in benzene (507 mL) using Dean-Stark conditions for 1h. After cooling, the reaction was quenched with saturated sodium bicarbonate solution (80 mL) and extracted with ethyl acetate (2 X 100mL). The combined organic layers were washed with brine (80 mL), dried over magnesium sulfate, filtered and concentrated. The

purification by silica gel column chromatography (Ethyl acetate 33% in hexane) furnished the target ketal (7.8 g, 97% yield). MS found: $(M+H)^+$ = 321.

(1e) The ketal from reaction (1d)(7.1 g, 22.3 mmol) and palladium hydroxide on carbon (20 wt%, 780 mg, 0.1 eq) were stirred in ethyl acetate (11 mL) under hydrogen (balloon) at rt for 45 min. After filtration and concentration, the target carboxylic acid (5.1 g, 99% yield) was obtained. MS found: $(M+H)^+$ = 231.

(1f) To a solution of the carboxylic acid from reaction (1e) (447 mg, 1.9 mmol) in acetone was added triethylamine (393 mg, 3.9 mmol) and ethyl chloroformate (316 mg, 2.9 mmol) at -25 °C under nitrogen. After stirring at rt for 10 min, sodium azide (316 mg, 4.9 mmol) dissolved in water (0.5 mL) was added to the mixture at -10 °C. The reaction was stirred at rt for 1h, and quenched with water (20 mL). It was extracted with CH_2Cl_2 (2 X 50 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. The crude azide was dissolved in benzene (2.6 mL) and refluxed for 1h. Benzyl alcohol (210 mg, 1.9 mmol) and p-toluenesulfonic acid (18 mg, 0.1 mmol) were added and the mixture was refluxed for 1h. After cooling to rt, the reaction was quenched with water and extracted with CH_2Cl_2 (2 X 50 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude was purified by silica gel column chromatography (33% EtOAc in hexane). The target amide (393 mg, 60% yield) was obtained. MS found: $(M+H)^+$ = 236.

(1g) The Cbz protected amine from reaction (1f) (3.8 g, 11.3 mmol), triethylamine (1.1 g, 11.3 mmol) and

palladium hydrooxide on carbon (20 wt%, 400 mg, 0.56 mmol) were stirred in EtOAc (57 mL) under hydrogen (50 psi) at rt for 2h. After filtration and concentration, the target amine was obtained (2.2 g, 96% yield). MS found: $(M+H)^+$ = 202.

(1h) To the solution of the amine from reaction (1g) (2.2 g, 11.3 mmol), 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid (3.49 g, 11.9 mmol) and diisopropylethylamine (3.7 g, 28.3 mmol) in DMF (57 mL) was added BOP reagent (6 g, 13.6 mmol) at 0 °C. After stirring at rt for 3h, the reaction was quenched with NH_4Cl (100 mL) at 0 °C, extracted with EtOAc (300 mL X 2), washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude (14g) was purified by silica gel column chromatography (Gradient elution ethyl acetate/hexane, 1:1 to ethyl acetate) to give the target compound amide (5.4 g, 99% yield). MS found: $(M+H)^+$ = 477.

(1i) Preparation of hydroxylamine/sodium methoxide solution: hydroxylamine hydrochloride (2.4 g, 34.5 mmol) and MeOH (9 mL) were heated to 55 °C. Sodium methoxide (25% wt in MeOH, 11.85 mL, 1.5 eq) was added, the mixture stirred at 55 °C for 5 minutes and cooled to room temperature then 0 °C. Filtration afforded a clear solution assumed to be ca. 1.64 M. The solution is prepared and used fresh.

A solution of 1.64 M hydroxylamine solution (4 mL, 20 eq) was added to the amine from reaction (36a) (300 mg, 0.63 mmol) in MeOH (3 mL) then stirred for 1h. The mixture was adjusted to pH 7 with 1 N hydrochloric acid (3 mL) providing a white precipitate. Filtration and drying provided the hydroxamic acid (220 mg, 73%, 2 steps). MS Found: $(M+H)^+$ = 478.

Example 2

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide trifluoroacetate

(2a) The ketone from reaction (1c) (3 g, 10.9 mmol) in dichloromethane (129 mL) was treated with allyltrimethyl silane (20 eq) and cooled to 0 °C. $TiCl_4$ (5 eq) was added dropwise over 30 min and the reaction allowed to warm to room temperature. The reaction was quenched by addition of ice and water and then extracted with dichloromethane, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography afforded the major diastereomer (943 mg, 29 %) MS found: $(M+H)^+$ = 319 and the minor diasteromer (236 mg, 7 %) MS found: $(M+H)^+$ = 319.

(2b). The major diastereomer from reaction (2a) (100 mg, 0.31 mmole) in tetrahydrofuran (1 mL) at 0 °C was treated with a solution of diborane (1M, 2 eq) and stirred for 30 min. The solution was quenched with hydrogen peroxide/sodium hydroxide (1:1, 3 eq ea) and then extracted with ethyl acetate. The organic layers were washed with water and brine, dried ($MgSO_4$) filtered and concentrated. Flash chromatogrophy yielded the desired alcohol (60 mg, 57%). MS found: $(M+H)^+$ = 337.

(2c) The alcohol from reaction (2b) (60 mg, 0.18 mmole) in dichloromethane (1 mL) was treated with triethyamine (2 eq) and methanesulfonylchloride (1.0 eq). The reaction was heated to reflux for 12 h and then partitioned between water and dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$) and

concentrated. Flash chromatography yielded the desired ester (34 mg, 60%). MS found: $(M+H)^+$ = 319.

(2d) Using procedures analogous to (1e)-(1g) and the ester from reaction (2c) (2.35 mg, 7.4 mmol) was converted to the desired acid, carbamate then amine (1.23 g, 85%, 3 Steps). MS found: $(M+H)^+$ = 200.

(2e) Using procedures analogous to (1h)-(1i) and the ester from reaction (2d) (1.2 g, 6.0 mmol) was converted to the desired hydroxamic acid (1.06 g, 30% yield, 2 steps). MS found: $(M+H)^+$ = 476.

Example 3

(5*S*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide trifluoroacetate

(3a) Using procedures analogous to (2b-e) the minor diastereomer from reaction (2a) (236 mg, 0.74 mmol) was converted to the desired hydroxamate (20 mg, 4% yield). MS found: $(M+H)^+$ = 476.

Example 4

(2*S*,3*R*)-*N*-hydroxy-3-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-6,10-dioxaspiro[4.5]decane-2-carboxamide

(4a) The ketal from reaction (1h) (47 mg, 0.1 mmol) in THF (0.4 mL) was treated with HCl (3N solution, 0.4 mL) at rt for 3h. The reaction was quenched with saturated NaHCO3 to basic solution at 0 °C. The mixture was extracted with ethyl acetate (20 mL X 2), washed with brine (10 mL), dried over Na_2SO_4, filtered, and

concentrated. Silica gel chromatography (dichloromethane/methanol, 20:1) provided the desired ketone (25 mg, 59 % yield). MS found: $(M+H)^+$ = 231.

(4b) The ketone from reaction (4a) (50 mg, 0.11 mmol) in benzene was treated with 1,3-propylene glycol and heated under Dean-Stark conditions to afford the desired ester (49 mg, 86 mmol). MS found: $(M+H)^+$ = 491.

(4c) Using conditions analogous to (1i), the ester from reaction (4ba) was converted to the desired hydroxamate (7 mg, 14 % yield). MS found: $(M+H)^+$ = 492.

Example 5

(7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methoxy]benzoyl}amino)-1,4-dithiaspiro[4.4]nonane-7-carboxamide trifluoroacetate

(5a) Using conditions analogous to (4b-c) the ketone from reaction (4a) (50 mg, 0.11 mmol) and 1,2-ethanedithiol were converted to the thiaketal and then the desired hydroxamic acid. MS found: $(M+H)^+$ = 510.

Example 6

(5*R*,7*S*,8*R*)-8-{[4-(2-butynyloxy)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(6a) Using analogous procedures to (1h-i) the amine from reaction (1g) (14 mg, 0.07 mmol) and 4-(2-butynyloxy)benzoic acid (15 mg, 1.1 eq) were converted to the desired amide and then hydroxamate. MS found: $(M+H)^+$ = 373.

Example 7

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(7a) 2-methylbenzimidazole (0.58 g, 4.36 mmol), methyl 4-(bromomethyl)-benzoate (1 g, 1 eq), cesium carbonate (2.13 g, 1.5 eq) in dimethylsulfoxide (4.4 mL) were stirred at room temperature for ca. 12 h. The mixture was partitioned between ethyl acetate and water. The layers were separated and the organic layer washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude material was purified on silica gel (ethyl acetate/methanol, 9:1) to give the desired ester as a white solid (0.77 g, 63%). MS found: $(M+H)^+$ = 281.

(7b) The ester from reaction (7a) (0.77 g, 2.75 mmol) in methanol (6.9 mL) was treated with lithium hydroxide (2N, 6.9 mL, 13.75 mmol) and stirred at rt for 2 h. The reaction was quenched with 1 N HCl (14 mL). The reaction was concentrated and extracted with ethyl acetate (2X), dried ($MgSO_4$), filtered and concentrated to give the desired acid (230 mg, 31%). MS found: $(M+H)^+$ = 267.

(7c) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (50 mg, 0.25 mmol) and the acid from reaction (7b) (80 mg, 1.2 eq) were converted to the desired amide then hydroxamate (67 mg, 48% 2 steps). MS found: $(M+H)^+$ = 449.

Example 8

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-isopropyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(8a) Using analogous procedures to (7a)-(7b) 2-isopropylbenzimidazole (698 mg, 4.36 mmol) and methyl 4-(bromomethyl)-benzoate (1 eq) were converted to the desired acid (446 mg, 28% yield, 2 steps). MS found: $(M+H)^+$ = 295.

(8b) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (54 mg, 0.27 mmol) and the acid from reaction (8a) (95 mg, 1.2 eq) were converted to the desired amide then hydroxamate (50 mg, 50% 2 steps). MS found: $(M+H)^+$ = 477.

Example 9

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide

(9a) Using analogous procedures to (7a)-(7b), 2-trifluormethylbenzimidazole (685 mg, 2.99 mmol) and methyl 4-(bromomethyl)-benzoate (1 eq) were converted to the desired acid (1 g, 99% yield, 2 steps). MS found: $(M+H)^+$ = 321.

(9b) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (49 mg, 0.25 mmol) and the acid from reaction (9a) (86 mg, 1.1 eq) were converted to the desired amide then hydroxamate (47 mg, 38% 2 steps). MS found: $(M+H)^+$ = 503.

Example 10

(5*R*,7*S*,8*R*)-8-({4-[(2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(10a) Using analogous procedures to (7a)-(7b), 2-*t*-butylbenzimidazole (1.6 g, 9.3 mmol) and methyl 4-(bromomethyl) benzoate (1 eq) were converted to the desired acid (1.9 g, 66% yield, 2 steps). MS found: $(M+H)^+$ = 309.

(10b) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (64 mg, 0.32 mmol) and the acid from reaction (10a) (120 mg, 1.2 eq) were converted to the desired amide then hydroxamate (93 mg, 40% 2 steps). MS found: $(M+H)^+$ = 492.

Example 11

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-1*H*-indol-3-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(11a) To a solution of trifluoroacetic acid (TFA) (1.16 mL, 15 mmol) in CH_2Cl_2 and triethylsilane (4.79 mL, 30 mmol) was added a solution of methyl 4-formylbenzoate (1.81 g, 11 mmol) and 2-methylindole (1.31 g, 10 mmol). The reaction was stirred 10 min at 0 °C and then quenched by adding the reaction solution to NaOH. Additional NaOH was added to get the pH to 8. The aqueous layer was extracted with EtOAc (1 x 100 mL) to obtain the crude compound. The crude was purified by silica gel chromatography (hexanes to 25% EtOAc/hexanes) to yield the desired ester (2.18 g, 78%). MS found: $(M+Na)^+$ = 302.

(11b) To a suspension of (11a) (1.79 mmol, 500 mg) in MeOH (5 mL) was added LiOH (0.9 mL, 1.79 mmol, 2M solution). The reaction was stirred for 16 h and then quenched to pH 7 with HCl (1N). The reaction mixture was

filtered to afford the desired acid (475 mg, 100%). MS found: $(M+H)^+$ = 266.

(11c) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (42 mg, 0.21 mmol) and the acid from reaction (11b) (86 mg, 1.1 eq) were converted to the desired amide then hydroxamate (3 mg, 3% 2 steps). MS found: $(M+H)^+$ = 448.

Example 12

(5*R*,7*S*,8*R*)-8-[(4-{[2-(difluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(12a) Using analogous procedures to (7a)-(7b), 2-(difluoromethyl)-benzimidazole (2.41 g, 11 mmol) was converted to the desired acid (1.47 mg, 49% yield,2 steps). MS found: $(M+H)^+$ = 303.

(12b) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (48 mg, 0.24 mmol) and the acid from reaction (11b) (81 mg, 1.1 eq) were converted to the desired amide then hydroxamate (35 mg, 28% 2 steps). MS found: $(M+H)^+$ = 485.

Example 13

(5*R*,7*S*,8*R*)-8-({4-[(2-cyclopropyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(13a) 2-cyclopropanecarboxylic acid (4 g, 52 mmol) was treated with phenylenediamine bis-hydrochloride (1 eq) and polyphosphosphoric acid (52 mL) and heated to 160 °C for 6 h. The reaction was cooled to 0 °C and diluted with

water, then basified with NaOH (50% aqueous) until pH >10. The solution was extracted with ethyl acetate, dried ($MgSO_4$), filtered and concentrated, purified by flash chromatography (100% ethyl acetate) giving 2-cyclopropylbenzimidazole (1.1 g, 13%). MS found: $(M+H)^+$ = 159.

(13b) Using analogous procedures to (7a)-(7b), 2-cyclopropylbenzimidazole (0.47 g, 3.0 mmol) was converted to the desired acid (375 mg, 43% yield, 2 steps). MS found: $(M+H)^+$ = 293.

(13c) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (52 mg, 0.26 mmol) and the acid from reaction (13b) (83 mg, 1.1 eq) were converted to the desired amide then hydroxamate (17 mg, 13% 2 steps). MS found: $(M+H)^+$ = 475.

Example 14

(5*R*,7*S*,8*R*)-8-({4-[(2-cyclobutyl-1*H*-benzimidazol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(14a) Using analogous procedures to (13a) 2-cyclobutanecarboxylic acid (5.2 g, 52 mmol) was converted to the desired benzimidazole (2.4 g, 27% yield).). MS found: $(M+H)^+$ = 173.

(14b) Using analogous procedures to (7a)-(7b), 2-cyclobutylbenzimidazole (1.0 g, 5.8 mmol) was converted to the desired acid (640 mg, 36% yield, 2 steps). MS found: $(M+H)^+$ = 307.

(14c) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (87 mg, 0.43 mmol) and the acid from reaction (14b) (135 mg, 1.0 eq) were converted to the desired amide then hydroxamate (50 mg, 23% yield, 2 steps). MS found: $(M+H)^+$ = 490.

Example 15

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-isopropyl-1*H*-imidazol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(15a) Using analogous procedures to (7a)-(7b), (1h)-(1i) 2-isopropylimidazole (1.1 g, 10 mmol) was converted to the desired hydroxamate acid (12 mg, 1% yield, 4 steps). MS found: $(M+H)^+$ = 427.

Example 16

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-1*H*-indol-1-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(16a) To a solution of 2-methylindole (7.60 mmol, 1.00 g) was added 18-crown-6 (60 mg, 0.06 mmol) and subsequently powdered KOH (416 mg, 7.60 mmol) and methyl 4-(bromomethyl)benzoate (1 eq). The reaction was heated to 100 °C for 2 h, and was added additional KOH (416 mg, 7.60 mmol). The reaction was stirred for another 1 h. The reaction was cooled and then quenched with 1N HCl and extracted with EtOAc (2 x 100 mL). The organic layers were collected, dried and concentrated in vacuo. The crude was flashed to yield the desired acid (798 mg, 40%). MS found: $(M+H)^+$ = 274.

(16b) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (39 mg, 0.2 mmol) and the acid from reaction (16a) (53 mg, 1 eq) were converted to the desired amide then hydroxamate (6 mg, 7%, 2 steps). MS found: $(M+H)^+$ = 448.

Example 17

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(1-methylcyclopropyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide

(17a) Using procedures similar to (1h), phenylenediamine bis-hydrochloride (6.9 g, 38 mmol) and 1-methyl-cyclopropanecarboxylic acid (3.8 g, 1 eq) were converted to the desired amide (4.0 g, 55%). MS found: $(M+H)^+$ = 191.

(17b) The amide from reaction (17a), (1.9 g, 10 mmol) in acetic acid (30 mL) was heated at 60 °C for 3 h. The mixture was concentrated, dissolved in ethyl acetate (20 mL), washed with saturated aqueous Na_2CO_3, saturated aqueous $NaHCO_3$, water, brine (10 mL each), dried ($MgSO_4$), filtered and concentrated to give the desired benzimidazole (1.7 g, 98%). MS found: $(M+H)^+$ = 173.

(17c) Using procedures analogous to (7a)-(7b), the product from reaction (17b) (1 g, 5.8 mmol) was converted to the desired acid (1.25 g, 70%, 2 steps). MS found: $(M+H)^+$ =307.

(17d) Using procedures analogous to (1h)-(1i),the product from reaction (17c) (56 mg, 0.18 mmol) and the amine from reaction (2d) (53 mg, 1 eq) were converted to the desired

hydroxamic acid (33 mg, 32%, 2 Steps). MS found: $(M+H)^+$ = 489.

Example 18

(5*R*,7*S*,8*R*)-8-[(4-{[2-(fluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(18a) Using procedures analogous to (17a)-(17c), fluoroacetic acid (2 g, 26 mmol) was converted to the desired acid (1.4 g, 12% yield, 3 steps). MS found: $(M+H)^+$ = 285.

(18b) Using procedures analogous to (1h)-(1i),the product from reaction (18a) (57 mg, 2 mmol) and the amine from reaction (2d) (40, 1 eq) were converted to the desired hydroxamic acid (34 mg, 29%, 2 Steps). MS found: $(M+H)^+$ = 467.

Example 19

(5*R*,7*S*,8*R*)-8-[(4-{[2-(1-fluoro-1-methylethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(19a) Ethyl-2-hydroxyisobutyrate (6 g, 45 mmol) in dichloromethane (60 mL) was treated with (diethylamino)sulfur trifluoride (DAST) (1.5 eq) at -78 °C, then warmed to rt and stirred for 2 h. The mixture was quenched with saturated $NaHCO_3$ (aq) and extracted with ethyl acetate, washed with water, brine, dried ($MgSO_4$) filtered and concentrated to give the desired ester (2.5 g, 41%). MS found: $(M+CH_3CN+H)^+$ = 176.

(19b) The solution of the ester for reaction (19a) (2.00 g, 14.9 mmol) in methanol (100 mL) was treated with potassium hydroxide (3.34 g, 4.0 eq) at rt and stirred for 24 hrs. Then the mixture was adjusted pH to 2-3 with 1N HCl and concentrated in vacuo to remove the methanol. The aqueous residue was extracted with ethyl acetate (100 mL, 3 times). The combined organic layers was washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to provide the desired acid (1.50 g, 94.8%) and taken on withoutfurther purification.

(19c) Using procedures analogous to (17a)-(17c) the acid from reaction (19b) (400 mg, 3.8 mmol) was converted to the desired acid (160 mg, 14%, 3 steps). MS found: $(M+H)^+$ = 313.

(19d) Using procedures analogous to (1h)-(1i), the product from reaction (19c) (47 mg, 0.15 mmol) and the amine from reaction (2d) (30 mg, 1 eq) were converted to the desired hydroxamic acid (30 mg, 33%, 2 Steps). MS found: $(M+H)^+$ = 495.

Example 20

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-{[4-(1*H*-indol-3-ylmethyl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxamide

(20a) Using procedures analogous to (11a)-(11b), (1h)-(1i) the amine from reaction (2d) (30 mg, 0.15 mmol) and indole (1 eq) were converted to the desired amide then hydroxamate (15 mg, 23%). MS found: $(M+H)^+$ = 435.

Example 21

(5*R*,7*S*,8*R*)-8-[(4-{[2-(1,1-difluoroethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(21a) Using analogous procedure to (19a) ethyl pyruvate (5.00 g, 43.1 mmol) was converted the desired ester as crude material (3.00 g) which was directly converted to the next step.

(21b) Using analogous procedure to (19b) -(19c) the ester from reaction (21a) (3.00 g) was converted to the desired acid (480 mg, 10.2% 6 steps). MS found: $(M+H)^+$ = 317.

(21c) Using procedures analogous to (1h) -(1i), the product from reaction (21b) (77.5 mg, 0.250 mmol) and the amine from reaction (2d) (50 mg, 1.0 eq) were converted to the desired hydroxamic acid (30.0 mg, 24% 2 steps). MS found: $(M+H)^+$ = 499.

Example 22

(5*R*,7*S*,8*R*)-8-({4-[(2,3-dimethyl-1*H*-indol-1-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(22a) To a solution of 2,3-dimethyl indole (1.0 g, 6.89 mmol) in DMF (30 mL) was added 18-crown-6 (56 mg, 0.21 mmol), KOH (386 mg, 6.89 mmol) and methyl 4-(bromomethyl)benzoate (1.58 g, 6.89 mmol). The reaction after flash chromatography afforded the desired ester (720 mg, 36%). MS found: $(M-Me+H)^+$ = 279.

(22b) Using a procedure analogous to (7b), the product from (22a) (2.45 mmol, 720 mg) was reacted to afford the acid (347 mg, 48%). MS found: $(M+H)^+$ = 280.

(22c) Using analogous procedures to (1h)-(1i) the amine from reaction (2d) (54 mg, 0.27 mmol) and the acid from reaction (22b) (40 mg, 1.0 eq) were converted to the desired amide then hydroxamate (15 mg, 23% 2 steps). MS found: $(M+H)^+$ = 462.

Example 23

(5*R*,7*S*,8*R*)-8-({4-[(2-ethyl-1*H*-indol-3-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(23a) Using procedures analogous to (11a)-(11c), 2-ethylindole (synthesized using the method of: Smith, A.B., III; Visnick, M.; Haseltine, J.N.; Sprengeler, P.A. Tetrahedron (1986), 42(11), 2957-69) (1.0 g, 6.9 mmol) was converted to the desired hydroxamate (40 mg, 11% yield, 4 steps). MS found: $(M+H)^+$ = 462.

Example 24

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(trifluoromethyl)-1*H*-indol-1-yl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide

(24a) Using procedures analogous to (16a)-(16b), 2-trifluoromethylindole ((synthesized using the method of: Smith, A.B., III; Visnick, M.; Haseltine, J.N.; Sprengeler, P.A. Tetrahedron (1986), 42(11), 2957-69) (98 mg, 6.9 mmol) was converted to the desired hydroxamate (10 mg, 7% yield, 4 steps). MS found: $(M+H)^+$ = 501.

Example 33

(5*R*,7*S*,8*R*)-8-{[4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(33a) Trifluoromethanesulfonic anhydride (2.2 mL, 13.4 mmol) was added dropwise to a stirring solution of thiochroman-4-one (2.0 g, 12.2 mmol), 2,6-di-t-butyl-4-methyl pyridine (2.63 g, 12.8 mmol) in dichloromethane (100 mL), under nitrogen atmosphere. The reaction was heated to reflux for 2 h, allowed to cool to room temperature and was concentrated in vacuo to give a semi-solid residue. This was treated with hexane and the solids were filtered off. The filtrate was concentrated to give 2*H*-1-benzothiopyran-4-yltrifluoromethyl sulfone (1.84 g, 51%) as a solid. MS found: $(M+H)^+$ = 297.

(33b) 2*H*-1-benzothiopyran-4-yl trifluoromethyl sulfone from reaction 33a (1.83 g, 6.17 mmol) and 4-(methoxy carbonylphenyl)boronic acid (1.11 g, 6.17 mmol) were dissolved in ethanol (15 mL) and toluene (30 mL) under nitrogen at room temperature. Then lithium chloride (0.52 g, 12.35 mmol) and 2.65 M potassium carbonate (4.66 mL, 12.35 mmol) were added. Nitrogen was bubbled through the reaction for 15 minutes tetrakis(triphenylphosphine)-palladium(0)(0.35 g, 0.31 mmol) was added. The reaction was heated to reflux for 2 h, allowed to cool then partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried over magnesium sulfate, and was concentrated. The product was purified by chromatography on silica gel eluting with ethyl acetate:hexane (15:85, v:v) to give methyl 4-(2*H*-1-benzothiopyran-4-yl)benzoate (1.75 g, 67%) as a solid.

(33c) Methyl 4-(2*H*-1-benzothiopyran-4-yl)benzoate from reaction 33b (0.77 g, 2.75 mmol) was dissolved in methanol (30 mL) cooled to 0 °C and Oxone® (6.76 g, 11.1 mmol) in water (7 mL) was added. The reaction was

stirred for 1 h at 0 °C and then allowed to warm to room temperature and stir for another hour. The reaction was diluted with water, pH adjusted to pH = 8 with 1 N sodium hydroxide. This was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over magnesium sulfate and concentrated to give methyl 4-(1,1-dioxido-2*H*-1-benzothiopyran-4-yl)benzoate (0.784 g, 91%) as a solid.

(33d) Methyl 4-(1,1-dioxido-2*H*-1-benzothiopyran-4-yl)benzoate from reaction 33c (0.64 g, 2.13 mmol) was dissolved in methanol (30 mL), degassed with nitrogen, 5% Pd/C was added and the reaction was charged to 55 PSI hydrogen. The reaction was shaken for 6 h. The catalyst was removed over Celite and the filtrate was concentrated to give methyl 4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoate (0.49 g, 73%) as a solid.

(33e) Lithium hydroxide hydrate (0.195 g, 4.65 mmol) dissolved in water (1 mL) was added to a solution of methyl 4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoate from reaction 33d (0.49 gm, 1.55 mmol) in THF (5 mL) and methanol (1 mL) under nitrogen atmosphere at room temperature. The reaction was stirred over night, concentrated then partitioned between 1 N HCl and ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to give 4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoic acid (0.46 g, 98%) as an solid. MS found: $(M-H)^+$ = 301.

(33f) 4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoic acid from reaction 33e (0.05 g, 0.165 mmol), the amine from reaction (2d)(0.030 g, 0.15 mmol), BOP (0.1 g, 0.22 mmol) and DIEA (0.058 g, 0.45 mmol) were combined in DMF (2 mL), under a nitrogen atmosphere at room temperature. The reaction was stirred for 48 h, partitioned between ethyl acetate and water. The

combined organic layers were washed with water, brine, dried over magnesium sulfate and concentrated to give methyl (5*R*,7*S*,8*R*)-8-{[4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxylate (0.07 g, 90%) as a tan solid.

(33g) Methyl (5*R*,7*S*,8*R*)-8-{[4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxylate from reaction 33f (0.165 mmol) was dissolved in a solution of hydroxylamine hydrochloride, methanol and sodium methoxide, (2 mL) under nitrogen atmosphere at room temperature. The reaction was stirred for 1 h, made neutral with TFA, concentrated and purified by HPLC on a C-18 column eluting with an acetonitrile: water: TFA gradient, to give the title compound (0.03 g, 37%) as a white solid. MS found: $(M+H)^+$ = 485, $(2M+H)^+$ =969.

Example 34

(5*R*,7*S*,8*R*)-8-{[4-(3,4-dihydro-2*H*-chromen-4-yl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(34a) Trifluoromethanesulfonic anhydride (1.2 mL, 7.4 mmol)was added drop wise to a stirring solution of chroman-4-one (1.0 g, 6.7 mmol), 2,6-di-t-butyl-4-methyl pyridine (1.59 g, 7.7 mmol) in dichloromethane (40 mL), under nitrogen atmosphere. The reaction was heated to reflux for 2 h, allowed to cool to room temperature and was concentrated in vacuo to give a semi solid residue. This was treated with hexane and the solids were filtered off. The filtrate was concentrated to give 4-[(trifluoromethyl)sulfonyl]-2*H*-chromene (1.78 g, 94%) as an orange oil.

(34b) 4-[(trifluoromethyl)sulfonyl]-2*H*-chromene from reaction 34a (1.78 g, 6.47 mmol) and 4-(methoxy carbonylphenyl) boronic acid (1.0 g, 5.6 mmol) were

dissolved in ethanol (15 mL) and toluene (30 mL) under nitrogen at room temperature. Then lithium chloride (0.52 g, 12.35 mmol) and 2.65 M potassium carbonate (4.2 mL, 11.0 mmol) were added. Nitrogen was bubbled through the reaction for 15 minutes before the tetrakis(triphenylphosphine)palladium(0) (0.35 g, 0.31 mmol) was added. The reaction was heated to reflux for 3 h, allowed to cool then partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried over magnesium sulfate, and was concentrated. The product was purified by chromatography on silica gel eluting with ethyl ether: hexane (20:80, v:v) to give methyl 4-(2*H*-chromen-4-yl)benzoate (1.53 g, 99%) as a yellow solid.

(34c) Lithium hydroxide hydrate (0.80 g, 19.0 mmol) dissolved in water (20 mL) was added to a solution of methyl 4-(2*H*-chromen-4-yl)benzoate from reaction 34b (1.5 gm, 5.7 mmol) in THF (20 mL) and methanol (20 mL) under nitrogen atmosphere at room temperature. The reaction was heated to 50 °C for 2 h, allowed to cool, concentrated then partitioned between 1 N HCl and ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to give 4-(2*H*-chromen-4-yl)benzoic acid (1.29 g, 89%) as a tan solid. MS found: $(M-H)^+ = 251$.

(34d) Thionyl chloride (2 mL) was added to a suspension of 4-(2*H*-chromen-4-yl)benzoic acid from reaction 34c (0.415 g, 1.6 mmol) in dichloromethane (10 mL) at room temperature. The reaction was stirred for 4 h, concentrated in vacuo to give 4-(2*H*-chromen-4-yl)benzoyl chloride (0.445 g, 99%) as a yellow solid.

(34e) Water saturated sodium bicarbonate (10 mL) was added to a solution of 4-(2*H*-chromen-4-yl)benzoyl chloride from reaction 34d (0.15 g, 0.55 mmol) and the

amine from reaction (2d)(0.120 g, 0.60 mmol) in benzene (10 mL). The reaction was stirred vigorously for 3 h, then partitioned between ethyl acetate and 1 N HCl. The combined organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to give methyl (5*R*,7*S*,8*R*)-8-{[4-(2*H*-chromen-4-yl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxylate (0.23 g, 96%) as a yellow oil. MS found: $(M+H)^+$ = 434.

(34f) Methyl (5*R*,7*S*,8*R*)-8-{[4-(2*H*-chromen-4-yl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxylate from reaction 34e (0.12 g, 0.29 mmol) was dissolved in methanol (30 mL), degassed with nitrogen, 5% Pd/C was added and the reaction was charged to 55 psi hydrogen. The reaction was shaken for 6 h. The catalyst was removed over Celite and the filtrate was concentrated to give methyl (5*R*,7*S*,8*R*)-8-{[4-(3,4-dihydro-2*H*-chromen-4-yl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxylate (0.10 g, 80%) as a clear oil.

(34g) Methyl (5*R*,7*S*,8*R*)-8-{[4-(3,4-dihydro-2*H*-chromen-4-yl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxylate from reaction 34f (0.095 g, 0.22 mmol) was dissolved in a solution of hydroxylamine hydrochloride, methanol and sodium methoxide, (2 mL) under nitrogen atmosphere at room temperature. The reaction was stirred for 1 h, made neutral with TFA, concentrated and purified by HPLC on a C-18 column eluting with an acetonitrile: water: TFA gradient, to give the title compound (0.032 g, 34%) as a white solid. MS found: $(M+H)^+$ = 435.

Example 35

(5*R*,7*S*,8*R*)-8-{[4-(2*H*-chromen-4-yl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(35a) (5*R*,7*S*,8*R*)-8-{[4-(2*H*-chromen-4-yl)benzoyl]amino}-1-oxaspiro[4.4]nonane-7-carboxylate from reaction (34e)

(0.10 g, 0.23 mmol) was dissolved in a solution of hydroxylamine hydrochloride, methanol and sodium methoxide, (2 mL) under nitrogen atmosphere at room temperature. The reaction was stirred for 1 h, made neutral with TFA, concentrated and purified by HPLC on a C-18 column eluting with an acetonitrile: water: TFA gradient, to give the title compound (0.032 g, 32%) as a white solid. MS found: $(M-H)^+$ = 433.

Example 41

N-{(5*R*,7*R*,8*S*)-8-[(hydroxyamino)carbonyl]-1-oxaspiro[4.4]non-7-yl}-2-[(2-isopropyl-1*H*-benzimidazol-1-yl)methyl]-1,3-thiazole-4-carboxamide

(41a) 2-Isopropylbenzimidizole (5.0 g, 31.2 mmol) was added portionwise to a stirred suspension of sodium hydride (1.25 g, 60% in mineral oil, 31.2 mmol) in DMF. After 30 min at room temperature 2-chloroacetamide (4.37 g , 46.9 mmol) was added and the solution heated to 50°C for 18 h. The reaction was quenched with saturated NH_4Cl then concentrated to dryness. A mixture of water/chloroform (1/1, 100 mL) was added and mixture was stirred vigorously for 15 min. The resulting white solid 41a was collected and dried under vacuum (2.92 g, 43%). MS Found: $(M+H)^+$ = 218.

(41b) Lawesson's Reagent (5.23 g, 12.9 mmol) and 41a (2.81 g, 12.9 mmol) were refluxed in toluene for 2 h. The solution was cooled to room temperature and 1N NaOH (75 mL) was added to the mixture then stirred for 30 min. The basic solution was extracted with EtOAc (3X) then the combined organic fractions were washed with brine. After drying over $MgSO_4$ the solution was filtered and concentrated to dryness. The residue was purified by

flash chromatography to give 41b as a white solid (1.74 g, 59%). MS Found: $(M+H)^+$=234.

(41c) Sodium methoxide (28.5 g , 0.525 mol) was added, portion wise to a cooled solution (0 °C) of methyl chloroacetate (54.4 g, 0.50 mol) and methyl formate (31.5 g, 0.525 mol) in toluene maintaining the temperature of the reaction below 5 °C. The solution was allowed to stir at 0 °C for 4 h then warm to room temperature. Water (200 mL) was added and the organic layer was separated. The aqueous layer was washed with ether then neutralized with 1N HCl. The aqueous layer was extracted with ether (3X) then the combined organic fractions were dried over $MgSO_4$ and concentrated *in vacuo* to give 41c a pale yellow oil (30.06 g, 44%) that was carried forward without further purification.

(41d) A solution of 41b (1.74 g, 7.45 mmol) and 41c (5.08 g, 37.3 mmol) were refluxed in ethanol overnight. The mixture was concentrated to dryness and the residue partitioned between EtOAc and $NaHCO_3$. The aqueous layer was extracted with EtOAc (3X) and the combined organic fractions were washed in succession with water, $NaHCO_3$, and brine. After drying over $MgSO_4$, filtration, and concentration to dryness the residue was purified by flash chromatography to give 41d as a yellow oil (1.36 g, 58%). MS Found: $(M+H)^+$ = 316.

(41e) Lithium hydroxide monohydrate (0.30 g, 6.47 mmol) was dissolved in water (8 mL) then added to 41d (1.36 g, 4.31 mmol) in THF (16 mL). The solution was stirred overnight and water (80 mL) was added. The aqueous phase was washed with ether (2X) then neutralized by the

addition of 1N HCl. The resulting solid was filtered and dried under vacuum to provide 41e as a light yellow solid (1.31 g, 100%). MS Found: $(M+H)^+$ = 302.

(41f) DIEA (0.252 g, 1.96 mmol) was added to the amine from reaction 2d (0.078 g, 0.39 mmol), 41e (0.153 g, 0.51 mmol) and BOP reagent (0.19 g, 0.43 mmol) in DMF at room temperature. After stirring overnight the solution was concentrated *in vacuo*, then diluted with EtOAc. The solution was washed with water, $NaHCO_3$, and brine then dried over $MgSO_4$. After filtration and removal of the solvent the residue was purified by flash chromatography to give 41f as a clear oil (0.081 g, 43%). MS Found: $(M+H)^+$ = 483.

(41g) Sodium methoxide (11.9 mL, 25% in methanol, 52.0 mmol) was added in a slow stream to hydroxylamine hydrochloride (2.40 g, 34.5 mmol) in methanol (9 mL) at 55 °C. The mixture was stirred for 5 min then cooled to room temperature. The sodium chloride was filtered to give a 1.64 M solution of basic hydroxyl amine. An aliquot (2.05 mL, 3.36 mmol) was added in one portion to 41f (81 mg, 0.17 mmol) and stirred at room temperature for 20 min. The reaction was quenched with 1N HCl and solvent was removed *in vacuo*. The residue was purified by reverse phase HPLC (C-18, acetonitrile/water) to provide example 41 as a white powder (27 mg, 33%) after lyophilization. MS Found: $(M+H)^+$ = 484.

Example 42

(5*R*,7*S*,8*R*)-8-({4-[(3,5-dimethyl-1*H*-pyrazol-4-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(42a) Methyl 4-formylbenzoate (2.00 g, 12.2 mmol), acetyl acetone (1.16 g , 11.6 mmol), piperidine (48 μL, 0.48 mmol), and acetic acid (0.14 mL, 2.44 mmol) were combined in toluene (60 mL) and heated to reflux with a Dean Stark trap attached for water removal. The reaction was complete in 2.5 h, the Dean Stark trap was removed and the mixture allowed to cool to room temperature. Dilution with ethyl acetate (120 mL) was followed by washing with water, 10% citric acid, $NaHCO_3$ (2X), and brine. After drying over $MgSO_4$, the solution was filtered and evaporated, then the residue was purified by flash chromatography to provide 42a as a yellow oil (2.43 g, 85%). MS Found: $(M+H)^+$ = 247.

(42b) Methanol (60 mL) was added slowly to 42a (2.42 g, 9.83 mmol) and palladium on carbon (10%, 0.5 g) under a steady stream of nitrogen. A hydrogen balloon was attached via a three way stopcock and the atmosphere above the reaction was removed and replaced with hydrogen three times. After 1 h no starting material was detectable by TLC and the hydrogen was removed and replaced with nitrogen. The catalyst was filtered and the solvent removed by evaporation *in vacuo.* The residue was purified by flash chromatography to provide 42b (1.91 g, 78%) as a clear oil. MS Found: $(M+H)^+$ = 249.

(42c) Hydrazine hydrate (0.14 g, 2.76 mmol) and 42b (0.62 g, 2.51 mmol) were combined in methanol (15 mL) and heated to reflux for 1.5 h. The reaction was cooled to room temperature and the solvent removed *in vacuo.* The residue was purified by flash chromatography to provide 42c as a waxy solid (585 mg, 95%). MS Found: $(M+H)^+$ = 245.

(42d) Sodium hydroxide (0.33 g, 8.33 mmol) was dissolved in water (5 mL) then added to 42c (585 mg, 2.39 mmol) in methanol/THF (1/1, 10 mL). The solution was stirred overnight and solvent was removed *in vacuo*. The residue was taken up in water (20 mL) and the aqueous phase was washed with ether (2X) then neutralized by the addition of 1N HCl (8.3 mL). The resulting solid was filtered and dried under vacuum to provide the desired acid as a white solid (288 mg, 88%). MS Found: $(M+H)^+$ = 231.

(42e) N-Methylmorpholine (195 mg, 1.93 mmol) was added to the amine from reaction 2d (77 mg, 0.39 mmol), the acid from (42d) (89 mg, 0.39 mmol) and BOP reagent (188 mg, 0.430 mmol) in DMF at room temperature. After stirring overnight the solution was concentrated *in vacuo*, then diluted with EtAOc (25 mL). The solution was washed with water, $NaHCO_3$ (2X), and brine then dried over $MgSO_4$. After filtration and removal of the solvent the residue was purified by flash chromatography to give the desired ester as a clear oil (109 mg, 69%). MS Found: $(M+H)^+$ = 483.

(42f) Sodium methoxide (11.9 mL, 25% in methanol, 52.0 mmol) was added in a slow stream to hydroxylamine hydrochloride (2.40 g, 34.5 mmol) in methanol (9 mL) at 55 °C. The mixture was stirred for 5 min then cooled to room temperature. The sodium chloride was filtered to give a 1.64 M solution of basic hydroxyl amine. An aliquot (3 mL, 4.92 mmol) was added in one portion to 42e (109 mg, 0.26 mmol) and stirred at room temperature for 30 min. The pH was adjusted to 6 with 1N HCl and the mixture was stirred vigorously for 20 min. The resulting solid was filtered then dried under vacuum to give the

desired hydroxamate as a white solid (73 mg, 67%). MS Found: $(M+H)^+$ = 413.

Example 43

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(43) Example 43 was prepared in an analogous manner to example 42 substituting N-methyl hydrazine for hydrazine hydrate in step 42c. Example 43 was isolated as a white solid (79 mg, 80%). MS Found: $(M+H)^+$ = 427.

Example 51

(5*R*,7*S*,8*R*)-8-({4-[(1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(51a) K_2CO_3 (4.4 g, 31.9 mmol) and 1,2-dibromoethane (0.69 mL, 8.0 mmol) were added to a solution of 2-aminothiophenol (1.0 g, 8.0 mmol) in 20 mL of acetone at room temperature. The reaction mixture was stirred overnight. The insoluble material was filtered off and the solvent was removed under reduced pressure. The residue was purified on silica gel column to provide 3,4-dihydro-2*H*-1,4-benzothiazine (0.8 g, 66%). MS (ES^+): 152 (M+1).

(51b) K_2CO_3 (5.2 g, 37.7 mmol) and methyl 4-bromomethylbenzoate (2.8 g, 12.6 mmol) were added to a solution of (51a) (1.9 g, 12.6 mmol) in 20 mL of anhydrous DMF. The reaction mixture was heated to 80 °C overnight. After cooling down, the solid was filtered off and rinsed with DMF. The solvent was removed under

reduced pressure and the residue was purified on silica gel column to provide methyl 4-(2,3-dihydro-4*H*-1,4-benzothiazin-4-ylmethyl)benzoate (3.02 g, 80%). MS (ES^+): 300 (M+1).

(51c) A solution of oxone® (2.2 g, 3.54 mmol) in 20 mL of H_2O was added slowly to a solution of (51b) (2.12 g, 7.1 mmol) in 20 mL of MeOH. Upon completion of the reaction, the solution was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and dried over $MgSO_4$. After filtration and concentration, the residue was purified on silica gel column to provide methyl 4-[(1-oxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl]benzoate (1.39 g, 65%). MS (AP^+): 316 (M+1).

(51d) A solution of KOH (1N, 7.5 mL) was added to a solution of (51c) (1.25 g, 3.8 mmol) in 40 mL of MeOH and 40 mL of H_2O. The reaction mixture was heated to 60 °C overnight. Upon completion, the aliquot was neutralized with HCl (1N, 7.5 mL). The solvent was removed and the residue was dissolved in MeOH. After filtration and concentration, 4-(2,3-dihydro-4*H*-1,4-benzothiazin-4-ylmethyl)benzoic acid was obtained in quantitative yield. MS (AP^+): 318 (M+1).

(51e) The amine from reaction (2d) (30 mg, 0.15 mmol), diisopropylethylamine (87 mg, 0.11 mL, 0.67 mmol), and CH_2Cl_2 (2.0 mL) were added to a flask charged with (51d) (42 mg, 0.13 mmol). The whole mixture was cooled to 0 °C and then added BOP (71 mg, 0.23 mmol) in one portion. The resulting solution was stirred overnight and TLC showed completion of the reaction. The solution was directly loaded on silica gel column and purified to

provide the desired product (51e)(55 mg, 82%). MS (AP^+): 499 (M+1).

(51f) 1 mL of NH_2OH/NaOMe/MeOH (1.64 M) was added to a flask charged with the product from (51e) (55 mg, 0.11 mmol) at 0 °C. The mixture was stirred for 20 min before it was quenched with 1 mL of aqueous HCl (1N). The resulting solution was then purified by reverse phase HPLC to provide the desired compound (51f)(50 mg, 90%). MS (ES^+): 522 (M+Na).

Example 52

(5*R*,7*S*,8*R*)-8-({4-[(2,2-dimethyl-1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(52a) K_2CO_3 (5.6 g, 40.9 mmol) and ethyl 2-bromoisobutyrate (6.0 mL, 40.9 mmol) were added to a solution of 2-aminothiophenol (5.12 g, 40.9 mmol) in 50 mL of anhydrous DMF at 0 °C. The mixture was stirred at 0 °C for 2 h and then heated to 100 °C for 10 h. After cooling down, the solid was filtered off and the solvent was stripped off. The resulting solid was washed with a mixture of dichloromethane and hexane (1:1) to provide the pure product (52a) (4.9 g, 62%). MS (AP^+): 194 (M+1).

(52b) To a solution of (52a) (2.0 g, 10.4 mmol) in 40 mL of anhydrous THF at -78 °C was added a solution of LAH in THF (1.0M, 10.4 mL). The reaction mixture was stirred overnight before it was quenched with ethyl acetate, MeOH and H_2O. The solution was extracted with ethyl acetate and the combined organic layer was dried over $MgSO_4$. After filtration and concentration, the residue was

purified on silica gel column to provide (52b) (1.5 g, 80%). MS (AP^+): 180 (M+1).

(52c) To a solution of (52b) (4.0 g, 22.3 mmol) in 50 mL of anhydrous THF at 0 °C was added NaH (1.1 g, 60% dispersion in mineral oil, 26.8 mmol). The mixture was stirred for 30 min before a solution of methyl 4-bromomethylbenzoate in 20 mL of anhydrous THF was added. The reaction was stirred overnight and was quenched with H_2O. The solution was extracted with ethyl acetate and washed with H_2O and brine, and dried over $MgSO_4$. After filtration and concentration, the residue was purified on silica gel to provide (52c) (5.2 g, 71%). MS (ES^+): 328 (M+1).

(52d) Following a procedure similar to (51c), the product from (52c) (2.3 g, 7.0 mmol) was converted to the corresponding sulfone (52d) (1.4 g, 56%). MS (ES^+): 719 (2M+1).

(52e) Following a procedure similar to (51d), the product from (52d) (1.4 g, 3.9 mmol) was converted to the corresponding acid (52e) in quantitative yield. MS (ES^+): 346 (M+1).

(52f) Following a procedure similar to (51e), the product from (52e) (46 mg, 0.13 mmol) was coupled with the amine from reaction (2d) (30 mg, 0.15 mmol) to provide (52f) (64 mg, 90%). MS (ES^+): 527(M+1).

(52g) Following a procedure similar to (51f), the product from (52f) (45 mg, 0.09 mmol) was converted to the

corresponding hydroxamate (52g)(40 mg, 89%). MS (ES^+): 550 (M+Na).

Example 53

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-methyl-4-quinolinyl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(53a) 2-hydroxy-4-methylquinoline (17.4 g, 109 mmol) and phosphorus oxytribromide (47.1 g, 164 mmol) were added to a round-bottom flask. The mixture was heated to 130 °C for several hours. After cooling down to room temperature, the residue was partitioned between saturated Na_2CO_3 and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 x 300 mL). The combined organic layer was washed with H_2O (2 x 400 mL) and brine (1 x 400 mL) and dried over $MgSO_4$. After filtration and concentration, the residue was purified on silica gel to provide 4-bromo-2-methylquinoline (53a)(8.8 g, 36%). MS (AP^+): 224 (M+1).

(53b) 4-Bromo-2-methylquinoline (53a) (1.0 g, 4.5 mmol) was dissolved in 10 mL of anhydrous THF and the resulting solution was cooled down to -78 °C. A solution of *n*-BuLi (3.0 mL, 1.6M, 4.8 mmol) was added slowly and the resulting solution was maintained at -78 °C for 5 min. Meanwhile, in another flask methyl 4-formylbenzoate (0.9 g, 5.4 mmol) was dissolved in 20 mL of anhydrous THF and the resulting solution was cooled to -78 °C before the lithium reagent made above was cannulated. The whole mixture was stirred for 30 min before quenched with MeOH. The solution was then diluted with ethyl acetate and

washed with H_2O and brine. After dried over $MgSO_4$, the organic solution was filtered and concentrated. The residue was purified on silica gel to provide methyl 4-[hydroxy(2-methyl-4-quinolinyl)methyl]benzoate (0.9 g, 65%). MS (AP^+): 308 (M+1).

(53c) The product from (53b) (105 mg, 0.34 mmol) was dissolved in 1 mL of dichloromethane. The solution was cooled to 0 °C and triethylamine (0.1 mL, 0.68 mmol) and MsCl (0.03 mL, 0.41 mmol) were added. The ice bath was removed and the reaction was monitored by TLC until the disappearance of starting material. The solution was diluted with ethyl acetate and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified to provide methyl 4-{(2-methyl-4-quinolinyl)[(methylsulfonyl)oxy]methyl} benzoate in quantitative yield. MS (AP^+): 386 (M+1).

(53d) A solution of (53c) (120 mg, 0.31 mmol) in 3 mL of MeOH was added to a suspension of the Pd/C catalyst (60 mg, 10%) in 2 mL of MeOH. The reaction took place after the flask was purged with H_2. The reaction was monitored using TLC until disappearance of the starting material. After filtered, the solution was concentrated and the residue was purified on silica gel to provide methyl 4-[(2-methyl-4-quinolinyl)methyl]benzoate in quantitative yield. MS (AP^+): 292 (M+1).

(53e) A solution of aqueous NaOH (1N, 35 mL) was added to a solution of (53d) (5.0 g, 17.2 mmol) in 100 mL of MeOH. The reaction mixture was heated up to 60 °C until completion of the reaction, monitored by TLC. Upon the completion, one equivalent of aqueous HCl (1N, 35 mL) was

added to neutralize the base. The solution was concentrated to dryness and the residue was redissolved in MeOH. After filtration, the methanolic solution was concentrated again to provide 4-[(2-methyl-4-quinolinyl)methyl]benzoic acid in quantitative yield. MS (ES^+): 278 (M+1).

(53f) The amine from reaction (2d) (29 mg, 0.14 mmol), diisopropylethylamine (74 mg, 0.1 mL, 0.6 mmol), dichloromethane (2.0 mL) and DMF (2.0 mL) were added to a flask charged with (53e) (40 mg, 0.14 mmol). The whole mixture was cooled to 0 °C and then BOP (76 mg, 0.17 mmol) was added in one portion. The resulting solution was stirred overnight and TLC showed completion of the reaction. The solution was directly loaded on silica gel column and flash chromatography provides the desired product (53f) (45 mg, 68%). MS (ES^+): 459 (M+1).

(53g) 1.0 mL of NH_2OH/NaOMe/MeOH at 0 °C was added to a flask charged with compound (53f) (40 mg, 0.09 mmol). The mixture was stirred for 20 min before it was quenched with 1.0 mL of aqueous HCl (1N). The resulting solution was purified by reverse phase HPLC to provide the desired compound(53g) as a TFA salt (53g) (15 mg, 30%). MS (ES^+): 460 (M+1).

Example 54

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-(trifluoromethyl)-4-quinolinyl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide

(54a) Following a procedure similar to (53a), 4-hydroxy-2-trifluoromethylquinoline (9.89 g, 46 mmol) was

converted to the corresponding bromide (12.5 g, 97%). MS (ES^+): 276 (M+1).

(54b) Following a procedure similar to (53b), the product from (54a)(1.0 g, 3.6 mmol) was converted to the corresponding product (54b)(0.38 g, 29%). MS (AP^+): 362 (M+1).

(54c) Following a procedure similar to (53c), the product from (54b) (360 mg, 1.0 mmol) was converted to the corresponding mesylate in quantitative yield. MS (AP^+): 440 (M+1).

(54d) Following a procedure similar to (53d), the product from (54c) (430 mg, 1.0 mmol) was reduced to the desired product (54d) in quantitative yield. MS (ES^+): 346 (M+1).

(54e) Following a procedure similar to (53e), the product from (54d) (340 mg, 1.0 mmol) was converted to the corresponding acid (54e) (320 mg, >95%). MS (AP^+): 332 (M+1).

(54f) Following a procedure similar to (53f), the product from (54e) (53 mg, 0.14 mmol) was coupled with the amine from reaction (2d) (30 mg, 0.17 mmol) to provide the desired product (54f) (43 mg, 57 %). MS (AP^+): 513 (M+1).

(54g) Following a procedure similar to (53g), the product from (54f) (23 mg, 0.045 mmol) was converted to the corresponding hydroxamate as a TFA salt (13 mg, 46%). MS (ES^+): 514 (M+1).

Example 55

(5*R*,7*S*,8*R*)-8-({4-[(2-ethyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(55a) To a flask were charged aniline (18.6 g, 0.2 mol), methyl propionylacetate (26.0 g, 0.2 mol), *p*-TsOH (0.3 g) and 100 mL of benzene. The mixture was heated to reflux and water was thus removed via Dean-Stark apparatus. After cooled down, insoluble material was filtered and the filtrate was concentrated to provide crude material in quantitative yield. The crude material was pure enough for next step. The crude material thus obtained was dissolved in 150 mL of Ph_2O and the solution was heated to 240 °C for 1 h. After cooled down, the solution was diluted with hexane and the precipitate (55a) (5.3 g, 15%) was collected. MS (ES^+): 174 (M+1).

(55b) Following a procedure similar to (53a), 4-hydroxy-2-ethylquinoline (55a)(5.0 g, 28.9 mmol) was converted to the corresponding bromide (3.6 g, 53%). MS (ES^+): 238 (M+1).

(55c) Following a procedure similar to (53b), the product from (55b) (3.0 g, 12.7 mmol) was converted to the desired product (55c) (2.82 g, 69%). MS (AP^+): 322 (M+1).

(55d) Following a procedure similar to (53c), the product from (55c) (3.0 g, 9.3 mmol) was converted to the corresponding mesylate (55d) in quantitative yield. MS (AP^+): 400 (M+1).

(55e) Following a procedure similar to (53d), the product from (55d) (3.7 g, 9.3 mmol) was reduced to the desired product (55e) (2.65g, 94%). MS (AP^+): 306 (M+1).

(55f) Following a procedure similar to (53e), the product from (55e) (2.6 g, 8.5 mmol) was converted to the corresponding acid (55f) (2.4 g, >95%). MS (ES^+): 292 (M+1).

(55g) Following a procedure similar to (53f), the product from (55f) (51 mg, 0.18 mmol) was coupled with the amine from reaction (2d) (35 mg, 0.18 mmol) to provide the desired product (55g) (80 mg, >95 %). MS (ES^+): 473 (M+1).

(55h) Following a procedure similar to (53g), the product from (55g) (80 mg, 0.17 mmol) was converted to the corresponding hydroxamate as a TFA salt (15 mg, 16%). MS (ES^+): 474 (M+1).

Example 56

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-({4-[(2-isopropyl-4-quinolinyl)methyl]benzoyl}amino)-1-oxaspiro[4.4]nonane-7-carboxamide

(56a) Malonic acid (4.1 g, 40 mmol) was mixed with phosphorus oxytribromide (35g) in an open vessel at 60 °C. Aniline (4.65 g) was carefully added in portion and the mixture was then heated at 130 °C for 3 h. The resulting tar-like material was cooled and carefully transfered into iced water. The solution was neutralized with 1N NaOH and the solid formed was collected. The solid was dissolved into dichloromethane and purified by

chromatography to provide 2,4-dibromoquinoline (5.2 g, 44%). MS (ES^+): 288 (M+1).

(56b) Tetrakis(triphenylphosphine)palladium (1.1 g, 1.0 mmol) and 2-propenylmagnesium bromide solution (0.5M, 10 mmol, 20 mL) were added to a solution of (56a) (2.9 g, 10.1 mmol) in 20 mL of THF at 0 °C. The reaction mixture was stirred at room temperature for 2 days and was quenched with MeOH. The solution was diluted with ethyl acetate and washed with H_2O and brine, and dried over $MgSO_4$. After filtration and concentration, the residue was purified to provide 4-bromo-2-isopropenylquinoline (56b) (1.54 g, 61%). MS (ES^+): 249 (M+1).

(56c) A solution of *n*-BuLi (2.5 M, 7.5 mmol, 3 mL) was added to a solution of (56b) (1.55 g, 6.25 mmol) in 20 mL of anhydrous THF at -78 °C. The resulting solution was cannulated to another flask charged with methyl 4-formylbenzoate (1.34 g, 8.1 mmol) in 20 mL of anhydrous THF at -78 °C. The reaction mixture was stirred for 3 h at -78 °C before quenched with MeOH. The solution was then diluted with ethyl acetate and washed with H_2O and brine, and dried over $MgSO_4$. After filtration and concentration, the residue was purified on silica gel column to provide methyl 4-[hydroxy(2-isopropenyl-4-quinolinyl)methyl]benzoate (0.95 g, 46%). MS (AP^+): 333 (M+1).

(56d) The product from (56c) (950 mg, 2.85 mmol) was dissolved in 100 mL of dichloromethane. The solution was cooled to 0 °C and triethylamine (2.0 mL, 14.3 mmol) and MsCl (0.44 mL, 5.7 mmol) were added. The ice bath was removed and the reaction been monitored by TLC until the

disappearance of starting material. The solution was diluted with ethyl acetate and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified to provide (56d) (1.0 g, >95%). MS (ES^+): 412 (M+1).

(56e) A solution of the mesylate from (56d) (1.0 g, 2.43 mmol) in 10 mL of MeOH and 10 mL of EtOAc was added to a suspension of the Pd/C catalyst (250 mg, 10 %) in 20 mL of MeOH. The reaction took place after the flask was purged with H_2. The reaction monitored by TLC until disappearance of the starting material. After filtered, the solution was concentrated and the residue was purified on silica gel to provide the desired product (56e) as a methanesulfuric acid salt (1.0 g, quantitative yield). MS (ES^+): 320 (M+1).

(56f) A solution of aqueous NaOH (1N, 5 mL) was added to a solution of (56e) (1.0g, 2.4 mmol) in 10 mL of MeOH. The reaction mixture was heated up to 60 °C until completion of the reaction, monitored by TLC. Upon the completion, one equivalent of aqueous HCl (1N, 5 mL) was added to neutralize the base. The solution was concentrated to dryness and the residue was redissolved in MeOH. After filtration, the methanolic solution was concentrated again to provide the desired product (56f) (700 mg, >95%). MS (ES^+): 306 (M+1).

(56g) Following a procedure similar to (53f), the product from (56f)(80 mg, 0.26 mmol) was coupled with the amine from reaction (2d) (52 mg, 0.26 mmol) to provide the desired product (56g) (65 mg, 51 %). MS (ES^+): 488 (M+1).

(56h) Following a procedure similar to (53g), the product from (56g) (60 mg, 0.12 mmol) was converted to the corresponding hydroxamate as a TFA salt (30 mg, 42%). MS (ES^+): 489 (M+1).

Example 57

(5*R*,7*S*,8*R*)-8-[(4-{[2-(dimethylamino)-4-quinolinyl]methyl}benzoyl)amino]-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(57a) 2,4-dibromoquinoline (56a)(2.0 g, 7.0 mmol) was dissolved in 10 mL of 40% dimethylamine solution in H_2O. The reaction mixture was allowed to stir overnight. The solution was diluted to 40 mL with H_2O and it was extracted with EtOAc for three times. The combined organic layer was dried over $MgSO_4$. After concentration, the residue was purified on silica gel column to provide 4-bromo-2-dimethylaminoquinoline (57a)(0.69 g, 40%). MS (AP^+): 251 (M+1).

(57b) Following a procedure similar to (53b), the product from (57a) (0.67 g, 2.7 mmol) was converted to methyl 4-[hydroxy(2-dimethylamino-4-quinolinyl)methyl]benzoate (57b) (0.15 g, 17%). MS (AP^+): 337 (M+1).

(57c) Following a procedure similar to (53c), the product from (57b) (0.15 g, 0.46 mmol) was converted to the corresponding mesylate in quantitative yield. MS (AP^+): 415(M+1).

(57d) Following a procedure similar to (53d), the product from (57c) (0.19 g, 0.46 mmol) was reduced to the desired product (57d) (106 mg, 57%). MS (AP^+): 321 (M+1).

(57e) Following a procedure similar to (53e), the product from (57d) (0.1 g, 0.26 mmol) was converted to the corresponding acid (57e) in quantitative yield. MS (ES^+): 307 (M+1).

(57f) Following a procedure similar to (53f), the product from (57e) (39 mg, 0.13 mmol) was coupled with the amine from reaction (2d) (31 mg, 0.15 mmol) to provide the desired product (57f) (31 mg, 50 %). MS (ES^+): 488 (M+1).

(57g) Following a procedure similar to (53g), the product from (57f) (31 mg, 0.06 mmol) was converted to the corresponding hydroxamate as a TFA salt (25 mg, 70%). MS (ES^+): 489 (M+1).

Example 58

(5*R*,7*S*,8*R*)-8-({4-[(2-cyclopropyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(58a) To a flask were charged aniline (6.55 g, 70 mmol), methyl 3-cyclopropyl-3-oxo-propionate(10.0 g, 70 mmol), *p*-TsOH (0.3 g) and 100 mL of benzene. The mixture was heated to reflux and water was thus removed via Dean-Stark apparatus. After cooled down, insoluble material was filtered and the filtrate was concentrated. The resulting residue was purified on silica gel column to provide the desired enamine product (58a) (4.5 g, 30%). MS (AP^+): 218 (M+1).

(58b) The material from (58a)(4.5 g, 0.021 mol) was dissolved in 50 mL of Ph_2O and the solution was heated to 240 °C for 1 h. After cooled down, the solution was

diluted with hexane and the precipitate (58b) (3.5 g, 90%) was collected. MS (AP^+): 186 (M+1).

(58c) To a solution of 4-hydroxy-2-cyclopropylquinoline (58b) (1.0 g, 5.4 mmol) in 50 mL of anhydrous THF at -78 °C was added LiHMDS (1.0 M, 5.4 mL, 5.4 mmol). The solution was stirred for 1 h, followed by addition of a solution of 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (2.33 g, 5.9 mmol) in 10 mL of THF. The mixture was allowed to warm to room temperature overnight. The reaction was quenched with 100 mL of H_2O and THF was removed under reduced pressure. The aqueous layer was extracted with EtOAc (4 x 75 mL) and the combined organic layer was dried over $MgSO_4$. After concentration, the residue was purified on silica gel column to provide the corresponding triflate (58c) (1.21 g, 79%). MS (ES^+): 318(M+1).

(58d) To a solution of (58c)(0.90 g, 3.1 mmol) in 15 mL of DMF were added LiCl (0.27 g, 6.3 mmol), $Pd(PPh_3)_4$ (0.36 g, 10 mol%, 0.31 mmol) and 4-(methoxycarbonyl)benzyl zinc bromide (0.5 M, 12.5 mL) (Shiota, T. *et al. J. Org. Chem.* **1999**, *64*, 453). The solution was stirred at room temperature overnight. DMF solvent was removed under reduced pressure and the residue was taken into 100 mL of H_2O. The aqueous phase was extracted by EtOAc (5 X 50 mL). The combined organic layer was washed with H_2O and saturated NaCl and dried over $MgSO_4$. After concentration, the residue was purified on silica gel column to give the desired product (58d) (0.45 g, 45%). MS (ES^+): 318 (M+1).

(58e) Following a procedure similar to (53e), the product from (58d) (0.57 g, 1.6 mmol) was converted to the corresponding acid (58e) (0.49 g, 84%). MS (ES^+): 304 (M+1).

(58f) Following a procedure similar to (53f), the product from (58e) (50 mg, 0.18 mmol) was coupled with the amine from reaction (2d) (36 mg, 0.18 mmol) to provide the desired product (58f) (72 mg, 90%). MS (ES^+): 485 (M+1).

(58g) Following a procedure similar to (53g), the product from (58f) (72 mg, 0.16 mmol) was converted to the corresponding hydroxamate as a TFA salt (64 mg, 66%). MS (ES^+): 486(M+1).

Example 59

(5*R*,7*S*,8*R*)-8-{[4-(1,3-dihydrofuro[3,4-*b*]quinolin-9-ylmethyl)benzoyl]amino}-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(59a) Following a procedure similar to (55a), methyl 4-oxotetrahydro-3-furancarboxylate (15.0 g, 0.1 mol) was condensed with aniline to provide the desired product (59a) (10.5 g, 56%). MS (ES^+): 188 (M+1).

(59b) Following a procedure similar to (58c), compound (59a) (1.0 g, 5.3 mmol) was converted to the corresponding triflate (59b) (850 mg, 50%). MS (ES^+): 320 (M+1).

(59c) Following a procedure similar to (58d), compound (59b) (850 mg, 2.66 mmol) was coupled with 4-(methoxycarbonyl)benzyl zinc bromide to provide the desired product (59c) (290 mg, 34%). MS (ES^+): 320 (M+1).

(59d) Following a procedure similar to (53e), the product from (59c) (0.29 g, 0.91 mmol) was converted to the corresponding acid (59d) (0.25 g, 86%). MS (ES^-): 304 (M-1).

(59e) Following a procedure similar to (53f), the product from (59d) (40 mg, 0.13 mmol) was coupled with the amine from reaction (2d) (26 mg, 0.13 mmol) to provide the desired product (59e) (60 mg, 94%). MS (ES^+): 487 (M+1).

(59f) Following a procedure similar to (53g), the product from (59e) (60 mg, 0.12 mmol) was converted to the corresponding hydroxamate as a TFA salt (32 mg, 44%). MS (ES^+): 488(M+1).

Example 60

(5*R*,7*S*,8*R*)-8-({4-[(2,3-dimethyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(60a) Ethyl 2-methylacetoacetate (28.8 g, 200 mmol) and catalytic *p*-toluenesulfuric acid were added to a solution of aniline (18.6 g, 200 mmol) in 200 mL of benzene. The mixture was heated to reflux and water generated in the reaction was collected. Upon the collection of theoretical amount of water, the solution was cooled and insoluble material was filtered off. After concentration of the organic solution, the crude material (60a) (39.0 g, 89%) was used for the next reaction. MS (ES^+): 220(M+1).

(60b) In a flask with distillation head and thermometer to monitor internal temperature was added 120 mL of

phenylether. In an additional funnel was charged a solution of (60a) (10.0 g, 45.6 mmol) in 20 mL of phenylether. The flask was preheated to 240 °C and the (60a) solution was added at such a rate that the inner temperature was maintained between 240-245 °C. After completion of the addition, the internal temperature of the flask was maintained at 245 °C for 25 min while distilling off ethanol. After cooling down the flask, the solid was filtered off and washed with hexane. The solid thus obtained is 2,3-dimethyl-4-hydroxyquinoline (7.5 g, 95%). MS (ES^+): 174(M+1).

(60c) Following a procedure similar to (53a), the product from (60b) (7.5 g, 43 mmol) was converted to 4-bromo-2,3-dimethylquinoline (6.87 g, 67%). MS (ES^+): 236 (M+1).

(60d) Following a similar procedure of (53b), 4-bromo-2,3-dimethylquinoline (3.4 g, 14.6mmol) was converted to methyl 4-[hydroxy(2,3-dimethyl-4-quinolinyl)methyl]benzoate (0.61 g, 13%). MS (ES^+): 322 (M+1).

(60e) Following a similar procedure of (53c), the product from (60d) (0.61 g, 1.9 mmol) was converted to methyl 4-{(2,3-dimethyl-4-quinolinyl)[(methylsulfonyl)oxy]methyl}benzoate (0.66 g, 87%). MS (ES^+): 400 (M+1).

(60f) Following a similar procedure of (53d), the product from (60e) was converted to methyl 4-[(2,3-dimethyl-4-quinolinyl)methyl]benzoate in quantitative yield. MS (AP^+): 306 (M+1).

(60g) Following a similar procedure of (53e), the product from (60f) was converted to 4-[(2,3-dimethyl-4-

quinolinyl)methyl]benzoic acid in quantitative yield. MS (AP^+): 292 (M+1).

(60h) Following a similar procedure of (53f), the acid from (60g) (47 mg, 0.14 mmol) was coupled with the amine from reaction (2d) (35 mg, 0.17 mmol) to provide the desired product (53 mg, 77%). MS (AP^+): 473 (M+1).

(60i) Following the procedure similar to (53g), the product from (60h) (50 mg, 0.11 mmol) was converted to the corresponding hydroxamate as a TFA salt (60i) (51 mg, 79%). MS (ES^+): 474 (M+1).

Example 61

(5*R*,7*S*,8*R*)-*N*-hydroxy-8-[(4-{[2-methyl-8-(trifluoromethyl)-4-quinolinyl]methyl}benzoyl)amino]-1-oxaspiro[4.4]nonane-7-carboxamide

(61a) Following a procedure similar to (55a), 2-trifluoromethylaniline (16.1 g, 0.1 mol) was condensed with methyl acetoacetate to provide the desired product (61a) (12.0 g, 53%). MS (ES^+): 228 (M+1).

(61b) Following a procedure similar to (58c), compound (61a) (1.0 g, 4.5 mmol) was converted to the corresponding triflate (61b)(1.49 g, 92%). MS (ES^+): 360 (M+1).

(61c) Following a procedure similar to (58d), compound (61b) (1.49 g, 4.15 mmol) was coupled with 4-(methoxycarbonyl)benzyl zinc bromide to provide the desired product (61c) (1.25 g, 83%). MS (ES^+): 360 (M+1).

(61d) Following a procedure similar to (53e), the product from (61c) (0.95 g, 2.65 mmol) was converted to the corresponding acid (61d) (0.90 g, >95%). MS (ES^+): 346 (M+1).

(61e) Following a procedure similar to (53f), the product from (61d) (40 mg, 0.11 mmol) was coupled with the amine from reaction (2d) (23 mg, 0.12 mmol) to provide the desired product (61e) (50 mg, 82%). MS (ES^+): 527 (M+1).

(61f)) Following a procedure similar to (53g), the product from (61e) (50 mg, 0.09 mmol) was converted to the corresponding hydroxamate as a TFA salt (64 mg, 95%). MS (ES^+): 528(M+1).

Example 62

(5*R*,7*S*,8*R*)-8-({4-[(3-ethyl-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(62a) Following a procedure similar to (60a), ethyl 2-ethylacetoacetate (31.6 g, 0.2 mol) was condensed with aniline to provide the desired enamine (62a) in quantitative yield. MS (AP^+): 235 (M+1).

(62b) Following a procedure similar to (60b), compound (62a) (10g, 43 mmol) was converted to the corresponding product (62b) (7.6 g, 95%). MS (AP^+): 188 (M+1).

(62c) Following a procedure similar to (53a), compound (62b) (7.5 g, 40 mmol) was converted to the corresponding bromide (6.4 g, 63%). MS (AP^+): 252 (M+1).

(62d) Following a procedure similar to (53b), compound (62c) (6.3 g, 25.2 mmol) was converted to the corresponding product (5.4 g, 64%). MS (AP^+): 377 ($M+CH_3CN+1$).

(62e) Following a procedure similar to (53c), compound (62d) (5.4 g, 16.1 mmol) was converted to the corresponding product (6.60 g, >95%). MS (AP^+): 414 (M+1).

(62f) Following a procedure similar to (53d), compound (62e) (6.6 g, 16.0 mmol) was reduced to the corresponding product (5.1 g, >95%). MS (AP^+): 350 ($M+CH_3CN+1$).

(62g) Following a procedure similar to (53e), compound (62f) (5.0 g, 15.7 mmol) was converted to the corresponding acid (3.4 g, 72%). MS (AP^+): 306 (M+1).

(62h) Following a procedure similar to (53f), compound (62f) (50 mg, 0.16 mmol) was coupled with the amine from reaction (2d) (33 mg, 0.16 mmol) to provide the desired product (62h) (70 mg, 87%). MS (ES^+): 487 (M+1).

(62i) Following a procedure similar to (53g), the product from (62h) (65 mg, 0.13 mmol) was converted to the corresponding hydroxamate as a TFA salt (40 mg, 60%). MS (ES^+): 488 (M+1).

Example 63

(5*R*,7*S*,8*R*)-8-({4-[(2,6-dimethyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(63a) Following a procedure similar to (55a), 4-methylaniline (21.4 g, 0.2 mol) was condensed with methyl acetoacetate to provide the desired product (63a) (22.0 g, 62%). MS (AP^+): 174 (M+1).

(63b) Following a procedure similar to (53a), compound (63a) (22 g, 127 mmol) was converted to the corresponding bromide (15.1 g, 50%). MS (AP^+): 236 (M+1).

(63c) Following a procedure similar to (53b), compound (63b) (10.0 g, 42.3 mmol) was converted to the corresponding product (8.4 g, 62%). MS (AP^+): 363 ($M+CH_3CN+1$).

(63d) Following a procedure similar to (53c), compound (63c) (8.4 g, 26.4 mmol) was converted to the corresponding mesylate in quantitative yield. MS (AP^+): 400 (M+1).

(63e) Following a procedure similar to (53d), compound (63d) (10.4 g, 26.0 mmol) was reduced to the corresponding product in quantitative yield. MS (AP^+): 306 (M+1).

(63f) Following a procedure similar to (53e), compound (63e) (8.0 g, 26.0 mmol) was converted to the corresponding acid (7.0 g, >95%). MS (ES^+): 292 (M+1).

(63g) Following a procedure similar to (53f), compound (63f)(50 mg, 0.17 mmol) was coupled with the amine from reaction (2d) (35 mg, 0.17 mmol) to provide the desired product (63g) (60 mg, 74%). MS (ES^+): 473 (M+1).

(63h) Following a procedure similar to (53g), the product from (63g) (60 mg, 0.13 mmol) was converted to the corresponding hydroxamate as a TFA salt (30 mg, 40%). MS (ES^+) 474 (M+1).

Example 64

(5*R*,7*S*,8*R*)-8-({4-[(6-chloro-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(64a) Following a procedure similar to (55a), 4-chloroaniline (25.5 g, 0.2 mol) was condensed with methyl acetoacetate to provide the desired product (64a) (17.6 g, 45%). MS (AP^+): 194 (M+1).

(64b) Following a procedure similar to (58c), compound (64a) (1.0 g, 5.16 mmol) was converted to the corresponding triflate (64b) (0.72 g, 43%). MS (AP^+): 326 (M+1).

(64c)) Following a procedure similar to (58d), compound (64b) (0.7 g, 2.15 mmol) was coupled with 4-(methoxycarbonyl)benzyl zinc bromide to provide the desired product (64c)(0.49 g, 70%). MS (AP^+): 326 (M+1).

(64d) Following a procedure similar to (53e), the product from (64c)(0.49 g, 1.5 mmol) was converted to the corresponding acid (64d) in quantitative yield. MS (AP^+): 312 (M+1).

(64e) Following a procedure similar to (53f), the product from (64d)(50 mg, 0.16 mmol) was coupled with the amine from reaction (2d) (32 mg, 0.16 mmol) to provide the

desired product (64e) in quantitative yield. MS (ES^+): 493 (M+1).

(64f)) Following a procedure similar to (53g), the product from (64e) (70 mg, 0.14 mmol) was converted to the corresponding hydroxamate as a TFA salt (40 mg, 47%). MS (ES^+): 494(M+1).

Example 65

(5*R*,7*S*,8*R*)-8-({4-[(6-fluoro-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(65a) Following a procedure similar to (55a), 4-fluoroaniline (11.1 g, 0.1 mol) was condensed with methyl acetoacetate to provide the desired product (65a) (10.5 g, 59%). MS (ES^+): 178(M+1).

(65b) Following a procedure similar to (58c), compound (65a) (2.0 g, 11.3 mmol) was converted to the corresponding triflate (65b) (1.93 g, 55%). MS (ES^+): 310 (M+1).

(65c)) Following a procedure similar to (58d), compound (65b) (0.38 g, 1.2 mmol) was coupled with 4-(methoxycarbonyl)benzyl zinc bromide to provide the desired product (65c) (0.13 g, 34%). MS (AP^+): 310 (M+1).

(65d) Following a procedure similar to (53e), the product from (65c) (0.13 g, 0.4 mmol) was converted to the corresponding acid (65d) (82 mg, 66%). MS (AP^+): 296 (M+1).

(65e) Following a procedure similar to (53f), the product from (65d) (40 mg, 0.13 mmol) was coupled with the amine from reaction (2d) (29 mg, 0.15 mmol) to provide the desired product (65e) (57 mg, 90%). MS (AP^+): 477 (M+1).

(65f) Following a procedure similar to (53g), the product from (65e) (54 mg, 0.11 mmol) was converted to the corresponding hydroxamate as a TFA salt (54 mg, 83%). MS (ES^+): 478(M+1).

Example 66

(5*R*,7*S*,8*R*)-8-({4-[(7-chloro-2-methyl-4-quinolinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(66a) Following a procedure similar to (55a), 3-chloroaniline (12.7 g, 0.1 mol) was condensed with methyl acetoacetate to provide the desired product (66a) (7.7 g, 79%). MS (AP^+): 194(M+1).

(66b) Following a procedure similar to (58c), compound (66a) (2.0 g, 10.3 mmol) was converted to the corresponding triflate (66b) (1.56 g, 46%). MS (AP^+): 326 (M+1).

(66c) Following a procedure similar to (58d), compound (66b) (1.5 g, 4.6 mmol) was coupled with 4-(methoxycarbonyl)benzyl zinc bromide to provide the desired product (66c) (0.47 g, 31%). MS (ES^+): 326 (M+1).

(66d) Following a procedure similar to (53e), the product from (66c) (0.47 g, 1.4 mmol) was converted to the

corresponding acid (65d) (375 mg, 84%). MS (ES^+): 353 ($M+CH_3CN+1$).

(66e) Following a procedure similar to (53f), the product from (66d) (50 mg, 0.16 mmol) was coupled with the amine from reaction (2d) (36 mg, 0.18 mmol) to provide the desired product (66e) (74 mg, 93%). MS (ES^+): 493 (M+1).

(66f)) Following a procedure similar to (53g), the product from (66e) (70 mg, 0.14 mmol) was converted to the corresponding hydroxamate as a TFA salt (50 mg, 59%). MS (ES^+): 494 (M+1).

Example 67

(5*R*,7*S*,8*R*)-8-({4-[(2,6-dimethyl-4-pyridinyl)methyl]benzoyl}amino)-*N*-hydroxy-1-oxaspiro[4.4]nonane-7-carboxamide

(67a) Following a procedure similar to (53a), 1*H*-pyridin-4-one (6.0 g, 48.7 mmol) was converted to the corresponding bromide (7.2 g, 79%). MS (ES^+): 186 (M+1).

(67b) Following a procedure similar to (53b), the product from (67a) (1.0 g, 5.4 mmol) was converted to the corresponding product (67b) (0.37 g, 25%). MS (ES^+): 272 (M+1).

(67c) Following a procedure similar to (53c), the product from (67b) (366 mg, 1.35 mmol) was converted to the corresponding mesylate (67c) in quantitative yield. MS (AP^+): 391 ($M+CH_3CN+1$).

(67d) Following a procedure similar to (53d), the product from (67c) (470 mg, 1.35 mmol) was reduced to the desired product (67d) in quantitative yield. MS (ES^+): 256 (M+1).

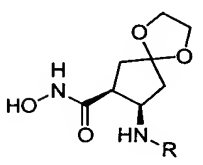
(67e) Following a procedure similar to (53e), the product from (67d) (460 mg, 1.34 mmol) was converted to the corresponding acid (67e) in quantitative yield. MS (AP^+): 242 (M+1).

(67f) Following a procedure similar to (53f), the product from (67e) (67 mg, 0.24 mmol) was coupled with the amine from reaction (2d) (58 mg, 0.29 mmol) to provide the desired product (67f) (45 mg, 44 %). MS (AP^+): 423 (M+1).

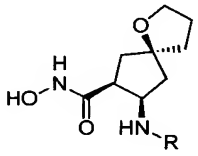
(67g) Following a procedure similar to (53g), the product from (67f) (45 mg, 0.11 mmol) was converted to the corresponding hydroxamate as a TFA salt (45 mg, 76%). MS (ES^+): 424 (M+1).

Table 1 below provides representative Examples, the synthesis of which is described above, of the compounds of the present invention.

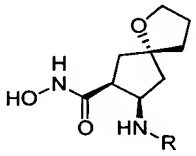
Table 1



Ex 1



Ex 2,6, 7-67



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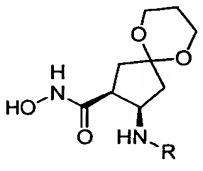

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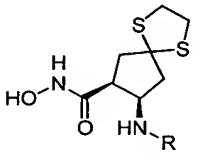


Ex 5

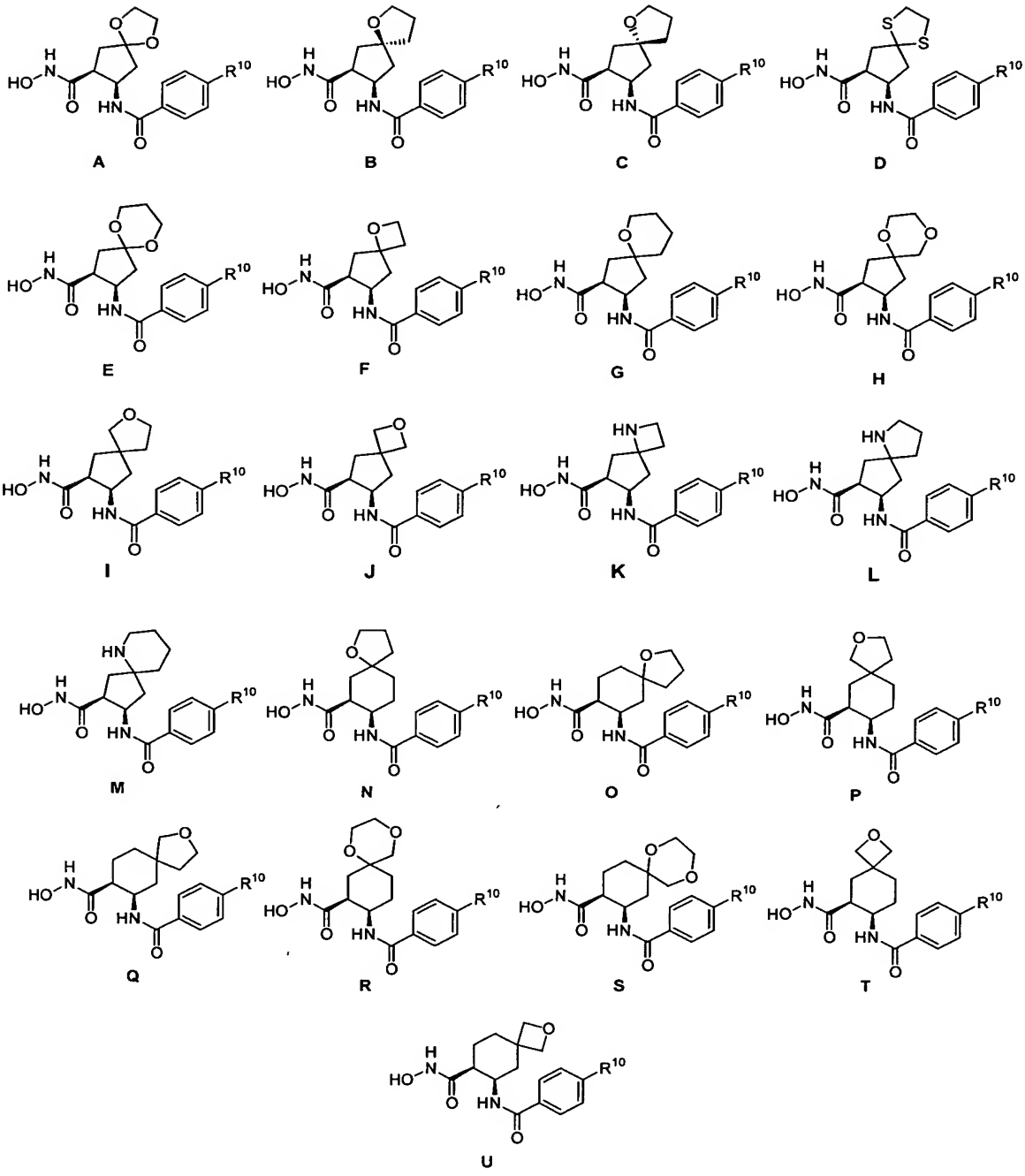
Ex	R	MS [M+H] or [M+Na]
1	4-(2-methyl-4-quinolinylmethoxy)benzoyl	478
2	4-(2-methyl-4-quinolinylmethoxy)benzoyl	476

3	4-(2-methyl-4-quinolinylmethoxy)benzoyl	476
4	4-(2-methyl-4-quinolinylmethoxy)benzoyl	492
5	4-(2-methyl-4-quinolinylmethoxy)benzoyl	510
6	4-(2-butynyloxy)benzoyl	393
7	4-[(2-methyl-1*H*-benzimidazol-1-yl)methyl]benzoyl	449
8	4-[(2-isopropyl-1*H*-benzimidazol-1-yl)methyl]benzoyl	477
9	4-{[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl	503
10	4-[(2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl]benzoyl	492
11	4-[(2-methyl-1*H*-indol-3-yl)methyl]benzoyl	448
12	4-{[2-(difluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl	485
13	4-[(2-cyclopropyl-1*H*-benzimidazol-1-yl)methyl]benzoyl	475
14	4-[(2-cyclobutyl-1*H*-benzimidazol-1-yl)methyl]benzoyl	490
15	4-[(2-isopropyl-1*H*-imidazol-1-yl)methyl]benzoyl	427
16	4-[(2-methyl-1*H*-indol-1-yl)methyl]benzoyl	448
17	4-{[2-(1-methylcyclopropyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl	489
18	4-{[2-(fluoromethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl	467
19	4-{[2-(1-fluoro-1-methylethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl	495
20	4-(1*H*-indol-3-ylmethyl)benzoyl	435
21	4-{[2-(1,1-difluoroethyl)-1*H*-benzimidazol-1-yl]methyl}benzoyl	499
22	4-[(2,3-dimethyl-1*H*-indol-1-yl)methyl]benzoyl	462
23	4-[(2-ethyl-1*H*-indol-3-yl)methyl]benzoyl	462
24	4-{[2-(trifluoromethyl)-1*H*-indol-1-yl]methyl}benzoyl	501
33	4-(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl)benzoyl	485
34	4-(3,4-dihydro-2*H*-chromen-4-yl)benzoyl	435
35	4-(2*H*-chromen-4-yl)benzoyl	433
41	2-[(2-isopropyl-1*H*-benzimidazol-1-yl)methyl]-1,3-thiazole-4-carboxyl	484

42	4-[(3,5-dimethyl-1*H*-pyrazol-4-yl)methyl]benzoyl	413
43	4-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl]benzoyl	427
51	4-[(1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl]benzoyl	522
52	4-[(2,2-dimethyl-1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl]benzoyl	550
53	4-[(2-methyl-4-quinolinyl)methyl]benzoyl	460
54	4-{[2-(trifluoromethyl)-4-quinolinyl]methyl}benzoyl	514
55	4-[(2-ethyl-4-quinolinyl)methyl]benzoyl	474
56	4-[(2-isopropyl-4-quinolinyl)methyl]benzoyl	489
57	4-{[2-(dimethylamino)-4-quinolinyl]methyl}benzoyl	489
58	4-[(2-cyclopropyl-4-quinolinyl)methyl]benzoyl	486
59	4-(1,3-dihydrofuro[3,4-*b*]quinolin-9-ylmethyl)benzoyl	488
60	4-[(2,3-dimethyl-4-quinolinyl)methyl]benzoyl	474
61	4-{[2-methyl-8-(trifluoromethyl)-4-quinolinyl]methyl}benzoyl	528
62	4-[(3-ethyl-2-methyl-4-quinolinyl)methyl]benzoyl	488
63	4-[(2,6-dimethyl-4-quinolinyl)methyl]benzoyl	474
64	4-[(6-chloro-2-methyl-4-quinolinyl)methyl]benzoyl	494
65	4-[(6-fluoro-2-methyl-4-quinolinyl)methyl]benzoyl	478
66	4-[(7-chloro-2-methyl-4-quinolinyl)methyl]benzoyl	494
67	4-[(2,6-dimethyl-4-pyridinyl)methyl]benzoyl	424

The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formula at the start of the table. For example, example 1 is intended to be paired with each of formulae A-J.

Table 2



Ex #	R^{10}
1	H
2	methyl
3	methoxy
4	1-methylethyl

5	1-methylethoxy
6	phenyl
7	[1,1'-biphenyl]-4-yl
8	phenoxy
9	2-phenylethyl
10	2-(3,5-dimethylphenyl)ethyl
11	1-(2,6-dimethylphenyl)ethyl
12	2-phenylethenyl
13	phenoxymethyl
14	(2-methylphenyl)methoxy
15	(3-methylphenyl)methoxy
16	3-methylphenoxy
17	2,6-dimethylphenoxy
18	(2,6-dimethylphenyl)methoxy
19	3,5-dimethylphenoxy
20	(3,5-dimethylphenyl)methoxy
21	2-(3,5-dimethylphenyl)ethyl
22	2-(3,5-dimethylphenyl)ethenyl
23	(3-amino-5-methylphenyl)methoxy
24	(2-amino-6-methylphenyl)methoxy
25	(3-cyano-5-methylphenyl)methoxy
26	(3-cyano-5-methylphenoxy)methyl
27	(3-cyano-5-nitrophenyl)methoxy
28	(3,5-diethoxyphenyl)methoxy
29	(3,5-dimethoxyphenyl)methoxy
30	3,5-dimethoxyphenoxy
31	2-(3,5-dimethoxyphenyl)ethyl
32	1-(3,5-dimethoxyphenyl)ethoxy
33	(3,5-dichlorophenyl)methoxy
34	(2,6-dichlorophenyl)methoxy
35	(3,5-dibromophenyl)methoxy
36	3,5-dibromophenoxy
37	(3-amino-5-cyanophenyl)methoxy
38	[2,6-bis(trifluoromethyl)phenyl]methoxy
39	2,6-bis(trifluoromethyl)phenoxy
40	(3-aminocarbonyl-5-methylphenyl)methoxy
41	([1,1'-biphenyl]-2-yl)methoxy
42	([1,1'-biphenyl]-3-yl)methoxy

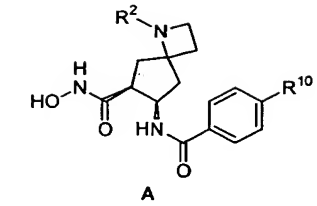
43	[5-methyl-3-(methylsulfonyl)phenyl]methoxy
44	5-methyl-3-(methylsulfonyl)phenoxy
45	(2-pyridinyl)methoxy
46	(4-pyridinyl)methoxy
47	(2,6-dimethyl-4-pyridinyl)methoxy
48	2,6-dimethyl-4-pyridinyloxy
49	1-(2,6-dimethyl-4-pyridinyl)ethoxy
50	(3,5-dimethyl-4-pyridinyl)methoxy
51	(2,6-diethyl-4-pyridinyl)methoxy
52	(2,6-dichloro-4-pyridinyl)methoxy
53	(2,6-dimethoxy-4-pyridinyl)methoxy
54	(2-chloro-6-methyl-4-pyridinyl)methoxy
55	(2-chloro-6-methoxy-4-pyridinyl)methoxy
56	(2-methoxy-6-methyl-4-pyridinyl)methoxy
57	(1-naphthalenyl)methoxy
58	1-naphthalenyloxy
59	(2-naphthalenyl)methoxy
60	(2-methyl-1-naphthalenyl)methoxy
61	(4-methyl-2-naphthalenyl)methoxy
62	(4-quinolinyl)methoxy
63	1-(4-quinolinyl)ethoxy
64	4-quinolinyloxy
65	(4-quinolinyloxy)methyl
66	2-(4-quinolinyl)ethyl
67	(2-methyl-4-quinolinyl)methoxy
68	2-methyl-4-quinolinyloxy
69	(2-chloro-4-quinolinyl)methoxy
70	(2-methoxy-4-quinolinyl)methoxy
71	(2-hydroxy-4-quinolinyl)methoxy
72	(2-trifluoromethyl-4-quinolinyl)methoxy
73	(2-phenyl-4-quinolinyl)methoxy
74	(2,6-dimethyl-4-quinolinyl)methoxy
75	(2,7-dimethyl-4-quinolinyl)methoxy
76	(5-quinolinyl)methoxy
77	(7-methyl-5-quinolinyl)methoxy
78	(7-methoxy-5-quinolinyl)methoxy
79	(8-quinolinyl)methoxy
80	2-(1,2,3-benzotriazol-1-yl)ethyl

81	(2-benzimidazolyl)methoxy
82	(1,4-dimethyl-5-imidazolyl)methoxy
83	(3,5-dimethyl-4-isoxazolyl)methoxy
84	(4,5-dimethyl-2-oxazolyl)methoxy
85	(2,5-dimethyl-4-thiazolyl)methoxy
86	(3,5-dimethyl-1-pyrazolyl)ethyl
87	(1,3-benzodioxo-4-yl)methoxy
88	(1,3,5-trimethyl-4-pyrazolyl)methoxy
89	(2,6-dimethyl-4-pyrimidinyl)methoxy
90	(4,5-dimethyl-2-furanyl)methoxy
91	(4,5-dimethyl-2-thiazolyl)methoxy
92	2-(2-oxazolyl)ethyl
93	2-butynyloxy
94	4-hydroxy-2-butynyloxy
95	4-pyridyl
96	4-pyridoxy
97	(2-methyl-4-quinolinyl)methylamino
98	3-phenyl-4,5-dihydro-5-isoxazolyl
99	3-(4-pyridinyl)-4,5-dihydro-5-isoxazolyl
100	5-(4-pyridinyl)-4,5-dihydro-3-isoxazolyl
101	(2-methyl-1*H*-benzimidazol-1-yl)methyl
102	(2-isopropyl-1*H*-benzimidazol-1-yl)methyl
103	[2-(trifluoromethyl)-1*H*-benzimidazol-1-yl]methyl
104	(2-*tert*-butyl-1*H*-benzimidazol-1-yl)methyl
105	(2-methyl-1*H*-indol-3-yl)methyl
106	[2-(difluoromethyl)-1*H*-benzimidazol-1-yl]methyl
107	(2-cyclopropyl-1*H*-benzimidazol-1-yl)methyl
108	(2-cyclobutyl-1*H*-benzimidazol-1-yl)methyl
109	(2-isopropyl-1*H*-imidazol-1-yl)methyl
110	(2-methyl-1*H*-indol-1-yl)methyl
111	[2-(1-methylcyclopropyl)-1*H*-benzimidazol-1-yl]methyl
112	[2-(fluoromethyl)-1*H*-benzimidazol-1-yl]methyl
113	[2-(1-fluoro-1-methylethyl)-1*H*-benzimidazol-1-yl]methyl
114	1*H*-indol-3-ylmethyl
115	[2-(1,1-difluoroethyl)-1*H*-benzimidazol-1-yl]methyl

116	(2,3-dimethyl-1*H*-indol-1-yl)methyl
117	(2-ethyl-1*H*-indol-3-yl)methyl
118	2-(trifluoromethyl)-1*H*-indol-1-yl]methyl
119	3,4-dihydro-2*H*-chromen-4-yl
120	1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-4-yl
121	2*H*-chromen-4-yl
122	(3,5-dimethyl-1*H*-pyrazol-4-yl)methyl
123	(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl
124	(1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl
125	(2,2-dimethyl-1,1-dioxido-2,3-dihydro-4*H*-1,4-benzothiazin-4-yl)methyl
126	(2-methyl-4-quinolinyl)methyl
127	[2-(trifluoromethyl)-4-quinolinyl]methyl
128	(2-ethyl-4-quinolinyl)methyl
129	(2-isopropyl-4-quinolinyl)methyl
130	[2-(dimethylamino)-4-quinolinyl]methyl
131	(2-cyclopropyl-4-quinolinyl)methyl
132	1,3-dihydrofuro[3,4-*b*]quinolin-9-ylmethyl
133	(2,3-dimethyl-4-quinolinyl)methyl
134	[2-methyl-8-(trifluoromethyl)-4-quinolinyl]methyl
135	3-ethyl-2-methyl-4-quinolinylmethyl
136	(2,6-dimethyl-4-quinolinyl)methyl
137	6-chloro-2-methyl-4-quinolinylmethyl
138	6-fluoro-2-methyl-4-quinolinylmethyl
139	7-chloro-2-methyl-4-quinolinylmethyl
140	2,6-dimethyl-4-pyridinylmethyl
141	2-methyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
142	2-ethyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
143	2-cyclopropyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
144	2-isopropyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
145	2-t-butyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
146	2-trifluoromethyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
147	2-difluoromethyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
148	2-fluoromethyl-pyrazolo[1,5-a]pyridin-3-ylmethyl
149	2-methyl-imidazo[1,2-a]pyridin-3-ylmethyl

150	2-ethyl-imidazo[1,2-a]pyridin-3-ylmethyl
151	2-isopropyl-imidazo[1,2-a]pyridin-3-ylmethyl
152	2-cyclopropyl-imidazo[1,2-a]pyridin-3-ylmethyl
153	2-t-butyl-imidazo[1,2-a]pyridin-3-ylmethyl
154	2-trifuoromethyl-imidazo[1,2-a]pyridin-3-ylmethyl
155	2-trifuoromethyl -imidazo[1,2-a]pyridin-3-ylmethyl
156	2-fluoromethyl-imidazo[1,2-a]pyridin-3-ylmethyl
157	2-methyl-1H-imidazo[4,5-b]pyridin-1-ylmethyl
158	2-ethyl-1H-imidazo[4,5-b]pyridin-1-ylmethyl
159	2-isopropyl-1H-imidazo[4,5-b]pyridin-1-ylmethyl
160	2-cyclopropyl-1H-imidazo[4,5-b]pyridin-1-ylmethyl
161	2-t-butyl-1H-imidazo[4,5-b]pyridin-1-ylmethyl
162	2-trifuoromethyl -1H-imidazo[4,5-b]pyridin-1-ylmethyl
163	2-difuoromethyl -1H-imidazo[4,5-b]pyridin-1-ylmethyl
164	2-fluoromethyl-1H-imidazo[4,5-b]pyridin-1-ylmethyl

Table 3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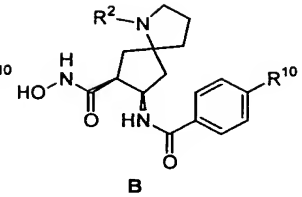
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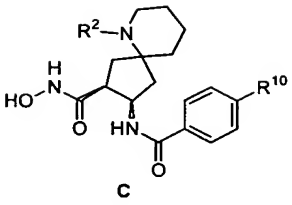
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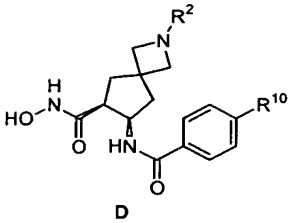
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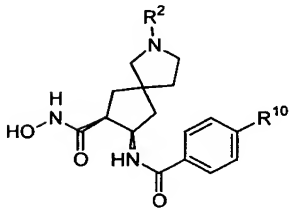
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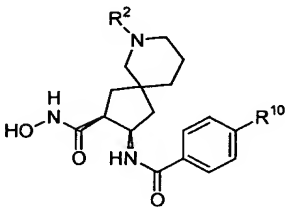
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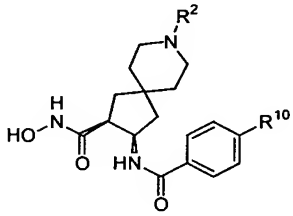
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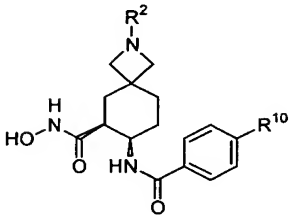
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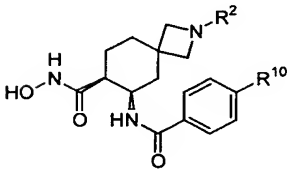
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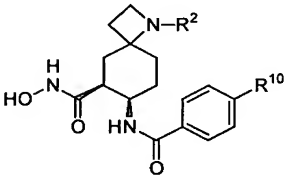
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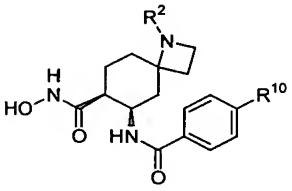
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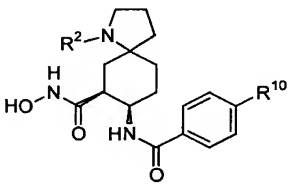
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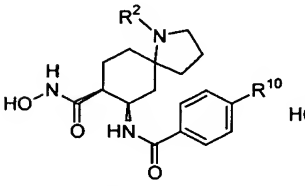
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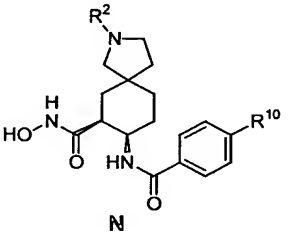
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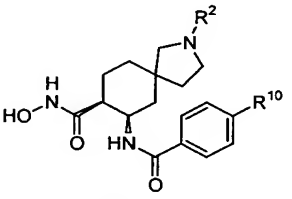
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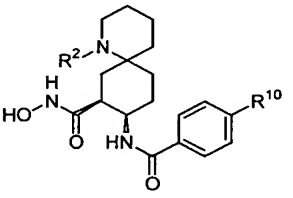
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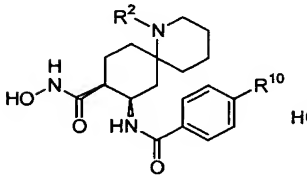
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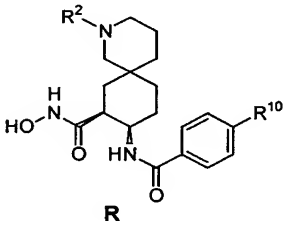
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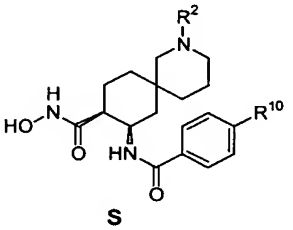
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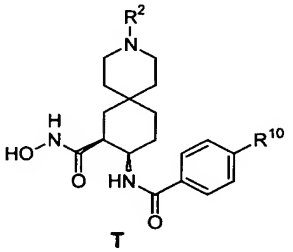
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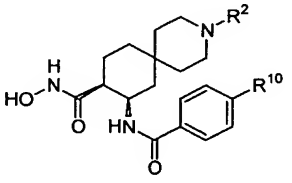
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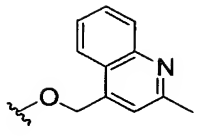

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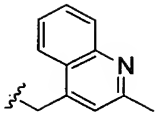

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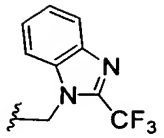

B3

Ex #	R^2	R^{10}
1	H	B1
2	methyl	B1
3	ethyl	B1
4	1-methylethyl	B1
5	cyclobutyl	B1
6	n-butyl	B1
7	2,2-dimethylpropyl	B1
8	cyclopropylmethyl	B1
9	2-methoxyethyl	B1
10	2-hydroxyethyl	B1
11	2-aminoethyl	B1
12	2-dimethylaminoethyl	B1
13	2-(4-morpholinyl)ethyl	B1
14	2-(1-piperidinyl)ethyl	B1
15	2-(1-piperizinyl)ethyl	B1
16	phenyl	B1
17	benzyl	B1
18	3-picolyl	B1
19	formyl	B1
20	acetyl	B1
21	pivaloyl	B1
22	benzoyl	B1
23	nicotinoyl	B1
24	methanesulfonyl	B1
25	benzenesulfonyl	B1
26	t-butylsulfonyl	B1
27	methoxycarbonyl	B1
28	t-butoxycarbonyl	B1
29	isopropyloxycarbonyl	B1
30	Dimethylcarbamyl	B1
31	4-morpholinecarbonyl	B1
32	2-thiophenecarbonyl	B1

33	2-fluoroethyl	B1
34	2,2-difluoroethyl	B1
35	2-(dimethylamino)-2-oxoethyl	B1
36	2-oxo-2-(4-morphorlinyl)ethyl	B1
37	tert-butyl	B1
38	1,1-dimethylpropyl	B1
39	2-propenyl	B1
40	1-methyl-2-propenyl	B1
41	1,1-dimethyl-2-propenyl	B1
42	2-propynyl	B1
43	1-methyl-2-propynyl	B1
44	1,1-dimethyl-2-propynyl	B1
45	(2-pyrrolidinyl)methyl	B1
46	H	B2
47	methyl	B2
48	ethyl	B2
49	1-methylethyl	B2
50	cyclobutyl	B2
51	n-butyl	B2
52	2,2-dimethylpropyl	B2
53	cyclopropylmethyl	B2
54	2-methoxyethyl	B2
55	2-hydroxyethyl	B2
56	2-aminoethyl	B2
57	2-dimethylaminoethyl	B2
58	2-(4-morpholinyl)ethyl	B2
59	2-(1-piperidinyl)ethyl	B2
60	2-(1-piperizinyl)ethyl	B2
61	phenyl	B2
62	benzyl	B2
63	3-picolyl	B2
64	formyl	B2
65	acetyl	B2
66	pivaloyl	B2
67	benzoyl	B2
68	nicotinoyl	B2
69	methanesulfonyl	B2
70	benzenesulfonyl	B2

71	t-butylsulfonyl	B2
72	methoxycarbonyl	B2
73	t-butoxycarbonyl	B2
74	isopropyloxycarbonyl	B2
75	Dimethylcarbamyl	B2
76	4-morpholinecarbonyl	B2
77	2-thiophenecarbonyl	B2
78	2-fluoroethyl	B2
79	2,2-difluoroethyl	B2
80	2-(dimethylamino)-2-oxoethyl	B2
81	2-oxo-2-(4-morphorlinyl)ethyl	B2
82	tert-butyl	B2
83	1,1-dimethylpropyl	B2
84	2-propenyl	B2
85	1-methyl-2-propenyl	B2
86	1,1-dimethyl-2-propenyl	B2
87	2-propynyl	B2
88	1-methyl-2-propynyl	B2
89	1,1-dimethyl-2-propynyl	B2
90	(2-pyrrolidinyl)methyl	B2
91	H	B3
92	methyl	B3
93	ethyl	B3
94	1-methylethyl	B3
95	cyclobutyl	B3
96	n-butyl	B3
97	2,2-dimethylpropyl	B3
98	cyclopropylmethyl	B3
99	2-methoxyethyl	B3
100	2-hydroxyethyl	B3
101	2-aminoethyl	B3
102	2-dimethylaminoethyl	B3
103	2-(4-morpholinyl)ethyl	B3
104	2-(1-piperidinyl)ethyl	B3
105	2-(1-piperizinyl)ethyl	B3
106	phenyl	B3
107	benzyl	B3
108	3-picolyl	B3

109	formyl	B3
110	acetyl	B3
111	pivaloyl	B3
112	benzoyl	B3
113	nicotinoyl	B3
114	methanesulfonyl	B3
115	benzenesulfonyl	B3
116	t-butylsulfonyl	B3
117	methoxycarbonyl	B3
118	t-butoxycarbonyl	B3
119	isopropyloxycarbonyl	B3
120	Dimethylcarbamyl	B3
121	4-morpholinecarbonyl	B3
122	2-thiophenecarbonyl	B3
123	2-fluoroethyl	B3
124	2,2-difluoroethyl	B3
125	2-(dimethylamino)-2-oxoethyl	B3
126	2-oxo-2-(4-morphorlinyl)ethyl	B3
127	tert-butyl	B3
128	1,1-dimethylpropyl	B3
129	2-propenyl	B3
130	1-methyl-2-propenyl	B3
131	1,1-dimethyl-2-propenyl	B3
132	2-propynyl	B3
133	1-methyl-2-propynyl	B3
134	1,1-dimethyl-2-propynyl	B3
135	(2-pyrrolidinyl)methyl	B3

UTILITY

The compounds of formula I are expected to possess matrix metalloprotease and/or aggrecanase and/or TNF-α inhibitory activity. The MMP inhibitory activity of the compounds of the present invention is demonstrated using assays of MMP activity, for example, using the assay described below for assaying inhibitors of MMP activity. The compounds of the present invention are expected to be bioavailable in vivo as demonstrated, for example, using the ex vivo assay described below. The compounds of formula I are expected to have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage degradation described below.

The compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MPs. These would be provided in commercial kits comprising a compound of this invention.

Metalloproteinases have also been implicated in the degradation of basement membranes to allow infiltration of cancer cells into the circulation and subsequent penetration into other tissues leading to tumor metastasis (Stetler-Stevenson, Cancer and Metastasis Reviews, 9, 289-303, 1990). The compounds of the present invention should be useful for the prevention and treatment of invasive tumors by inhibition of this aspect of metastasis.

The compounds of the present invention should also have utility for the prevention and treatment of osteopenia associated with matrix metalloproteinase-mediated breakdown of cartilage and bone that occurs in osteoporosis patients.

Compounds that inhibit the production or action of TACE and/or Aggrecanase and/or MMP's are potentially

useful for the treatment or prophylaxis of various inflammatory, infectious, immunological or malignant diseases or conditions. Thus, the present invention relates to a method of treating various inflammatory, infectious, immunological or malignant diseases. These include acute infection, acute phase response, age related macular degeneration, alcoholism, allergy, allergic asthma, anorexia, aneurism, aortic aneurism, asthma, atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia (including cachexia resulting from cancer or HIV), calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy (including inflammatory bowl disease), Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pulmonary emphysema, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis (including juvenile rheumatoid arthritis and adult rheumatoid arthritis), sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke,

systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

Some compounds of the present invention have been shown to inhibit TNF production in lipopolysacharride stimulated mice, for example, using the assay for TNF induction in mice and in human whole blood as described below.

Some compounds of the present invention have been shown to inhibit aggrecanase, a key enzyme in cartilage breakdown, as determined by the aggrecanase assay described below.

As used herein "μg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "μL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC_{50} or K_i value of less than about 10 μM for the inhibition of a desired MP. Preferred compounds of the present invention have K_i's or IC_{50}'s of $\leq$1 μM. More preferred compounds of the present invention have K_i's or IC_{50}'s of $\leq$0.1 μM. Even more preferred compounds of the present invention have K_i's or IC_{50}'s of $\leq$0.01 μM. Still more preferred compounds of the present invention have K_i's or IC_{50}'s of $\leq$0.001 μM.

Aggrecanase Enzymatic Assay

A novel enzymatic assay was developed to detect potential inhibitors of aggrecanase. The assay uses active aggrecanase accumulated in media from stimulated bovine nasal cartilage (BNC) or related cartilage sources

and purified cartilage aggrecan monomer or a fragment thereof as a substrate.

The substrate concentration, amount of aggrecanases time of incubation and amount of product loaded for Western analysis were optimized for use of this assay in screening putative aggrecanase inhibitors. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α) or other stimuli. Matrix metalloproteinases (MMPs) are secreted from cartilage in an inactive, zymogen form following stimulation, although active enzymes are present within the matrix. We have shown that following depletion of the extracellular aggrecan matrix, active MMPs are released into the culture media (Tortorella, M.D. et al. *Trans. Ortho. Res. Soc.* **1995**, *20*, 341). Therefore, in order to accumulate BNC aggrecanase in culture media, cartilage is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant IL-ß for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. In order to decrease the amount of other matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media, containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, C. E. et al., Biochem J 306:799-804, 1995). This antibody recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon

cleavage by aggrecanase. The BC-3 antibody recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Other proteases produced by cartilage in response to IL-1 do not cleave aggrecan at the Glu373-Ala374 aggrecanase site; therefore, only products produced upon cleavage by aggrecanase are detected. Kinetic studies using this assay yield a Km of 1.5 +/- 0.35 μM for aggrecanase.

To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water or other solvents and diluted to appropriate concentrations in water. Drug (50 ul) is added to 50 ul of aggrecanase-containing media and 50 ul of 2 mg/ml aggrecan substrate and brought to a final volume of 200 ul in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM $CaCl_2$. The assay is run for 4 hr at 37 °C, quenched with 20 mM EDTA and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background.

Removal of the glycosaminoglycan side chains from aggrecan is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 ug GAG) for 2 hr at 37 °C and then with keratanase (0.1 units/10 ug GAG) and keratanase II (0.002 units/10 ug GAG) for 2 hr at 37 °C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 μl of Tris glycine SDS sample buffer (Novex)

containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

TNF PBMC ASSAY

Human peripheral blood mononuclear cells (PBMC) were obtained from normal donor blood by leukophoresis and isolated by Ficoll-Paque density separation. PBMCs were suspended in 0.5 ml RPMI 1640 with no serum at 2 x 10^6 cells/ml in 96 well polystyrene plates. Cells were preincubated 10 minutes with compound, then stimulated with 1 µg/ml LPS (Lipopolysaccharide, Salmonella typhimurium) to induce TNF production. After an incubation of 5 hours at 37 °C in 95% air, 5% CO_2 environment, culture supernatants were removed and tested by standard sandwich ELISA for TNF production.

TNF Human Whole Blood Assay

Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10 ml. 225 µl of blood is plated directly into sterile polypropylene tubes. Compounds are diluted in DMSO/serum free media and added to the blood samples so the final concentration of compounds are 50, 10, 5, 1, 0.5, 0.1, and 0.01 µM. The final concentration of DMSO does not exceed 0.5%.

Compounds are preincubated for 15 minutes before the addition of 100 ng/ml LPS. Plates are incubated for 5 hours in an atmosphere of 5% CO_2 in air. At the end of 5 hours, 750 µl of serum free media is added to each tube and the samples are spun at 1200 RPM for 10 minutes. The supernatant is collected off the top and assayed for TNF-alpha production by a standard sandwich ELISA. The ability of compounds to inhibit TNF-alpha production by 50% compared to DMSO treated cultures is given by the IC_{50} value.

TNF Induction In Mice

Test compounds are administered to mice either I.P. or P.O. at time zero. Immediately following compound administration, mice receive an I.P. injection of 20 mg of D-galactosamine plus 10 µg of lipopolysaccharide. One hour later, animals are anesthetized and bled by cardiac puncture. Blood plasma is evaluated for TNF levels by an ELISA specific for mouse TNF. Administration of representative compounds of the present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

MMP ASSAYS

The enzymatic activities of recombinant MMP-1, 2, 3, 7, 8, 9, 10, 12, 13, 14, 15, and 16 were measured at 25 °C with a fluorometric assay (Copeland, R.A. et al. *Bioorganic Med. Chem. Lett.* **1995**, *5* , 1947-1952). Final enzyme concentrations in the assay were between 0.05 and 10 nM depending on the enzyme and the potency of the inhibitor tested. The permisive peptide substrate, MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH_2, was present at a final concentration of 10 µM in all assays. Initial velocities, in the presence or absence of inhibitor, were

measured as slopes of the linear portion of the product progress curves. IC50 values were determined by plotting the inhibitor concentration dependence of the fractional velocity for each enzyme, and fitting the data by non-linear least squares methods to the standard isotherm equation (Copeland, R.A. *Enzymes: A practical Introduction to Structure, Mechanism and Data Analysis*, Wiley-VHC, New York, **1996**, pp 187-223). All of the compounds studied here were assumed to act as competitive inhibitors of the enzyme, binding to the active site Zn atom as previously demonstrated by crystallographic studies of MMP-3 complexed with related hydroxamic acids (Rockwell, A. et al. *J. Am. Chem. Soc.* **1996**, *118*, 10337-10338). Based on the assumption of competitive inhibiton, the IC_{50} values were converted to Ki values as previously described.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of $\leq$10 μM. Preferred compounds of the present invention have K_i's of $\leq$1 μM. More preferred compounds of the present invention have K_i's of $\leq$0.1 μM. Even more preferred compounds of the present invention have K_i's of $\leq$0.01 μM. Still more preferred compounds of the present invention have K_i's of $\leq$0.001 μM.

Using the methodology described above, a number of compounds of the present invention were found to exhibit K_i's of $\leq$10 μM, thereby confirming the utility of the compounds of the present invention.

Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage

forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical

condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches wall known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or

carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any

unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of unit capsules may also prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150

milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Syrup

	Wt. %
Active Ingredient	10
Liquid Sugar	50
Sorbitol	20
Glycerine	5
Flavor, Colorant and Preservative	as required
Water	as required

The final volume is brought up to 100% by the addition of distilled water.

Aqueous Suspension

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.01
Keltrol® (Food Grade Xanthan Gum)	0.2
Liquid Sugar	5
Flavor, Colorant and Preservative	as required
Water	as required

Xanthan gum is slowly added into distilled water before adding the active ingredient and the rest of the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendable Powder

	Wt. %
Active Ingredient	50.0
Lactose	35.0
Sugar	10.0
Acacia	4.7
Sodium Carboxylmethylcellulose	0.3

Each ingredient is finely pulverized and then uniformly mixed together. Alternatively, the powder can be prepared as a suspension and then spray dried.

Semi-Solid Gel

	Wt. %
Active Ingredient	10
Sodium Saccharin	0.02
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

	Wt. %
Active Ingredient	10
Gelcarin® (Carrageenin gum)	1
Sodium Saccharin	0.01
Gelatin	2
Flavor, Colorant and Preservative	as required
Water	as required

Gelcarin® is dissolved in hot water (around 80°C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

	Wt. %
Active Ingredient	30
Tween® 80 and Span® 80	6
Keltrol®	0.5
Mineral Oil	63.5

All the ingredients are carefully mixed together to make a homogenous paste.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of tablets may also be prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely

divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's). The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the compound of Formula I and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above. Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated

with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.